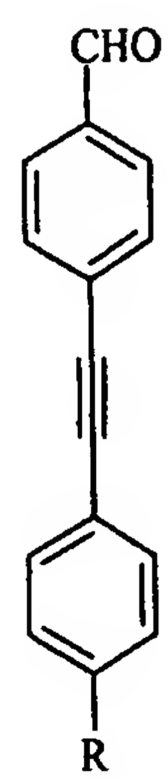
Method for preparing para-phenyl alkynyl benzaldehydes

Summary of the invention

The present invention is related to a new synthesis for preparing para-phenyl alkynyl benzaldehyde of general formula (I). The compounds of formula (I) are useful building blocks, in particular in the synthesis of drugs and electrically conducting polymers.

Field of the invention

The present invention is related to a new synthesis for preparing para-phenyl alkynyl benzaldehydes of general formula (I) :



(I)

R is selected from the group consisting of C_1-C_{12}–alkyl, C_1-C_{12}-alkyl aryl, C_1-C_{12}-alkyl heteroaryl, C_2-C_{12}-alkenyl, C_2-C_{12}-alkenyl aryl, C_2-C_{12}-alkenyl heteroaryl, C_2-C_{12}-alkynyl, C_2-C_{12}-alkynyl aryl, C_2-C_{12}-alkynyl heteroaryl, C_1-C_{12}–alkyl-C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl, C_1-C_{12}–alkoxy, aryl, heteroaryl, halides.

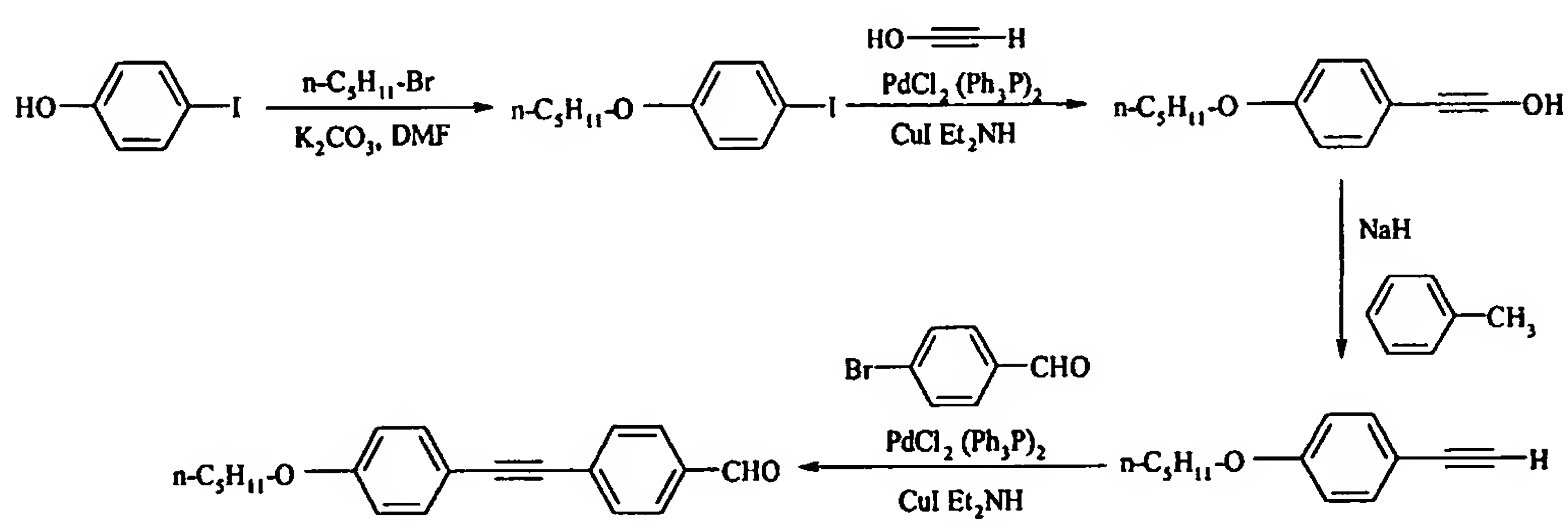
The method employs commercially available, or easily obtainable, starting compounds and comprises or consists of four steps.

Background of the invention

The synthetic approach for preparing para-phenyl alkynyl benzaldehydes is well known. Several documents quote the use of para-phenyl alkynyl benzaldehydes as building block in the synthesis of various compounds, e.g. for the synthesis of electrically conductive polymers.

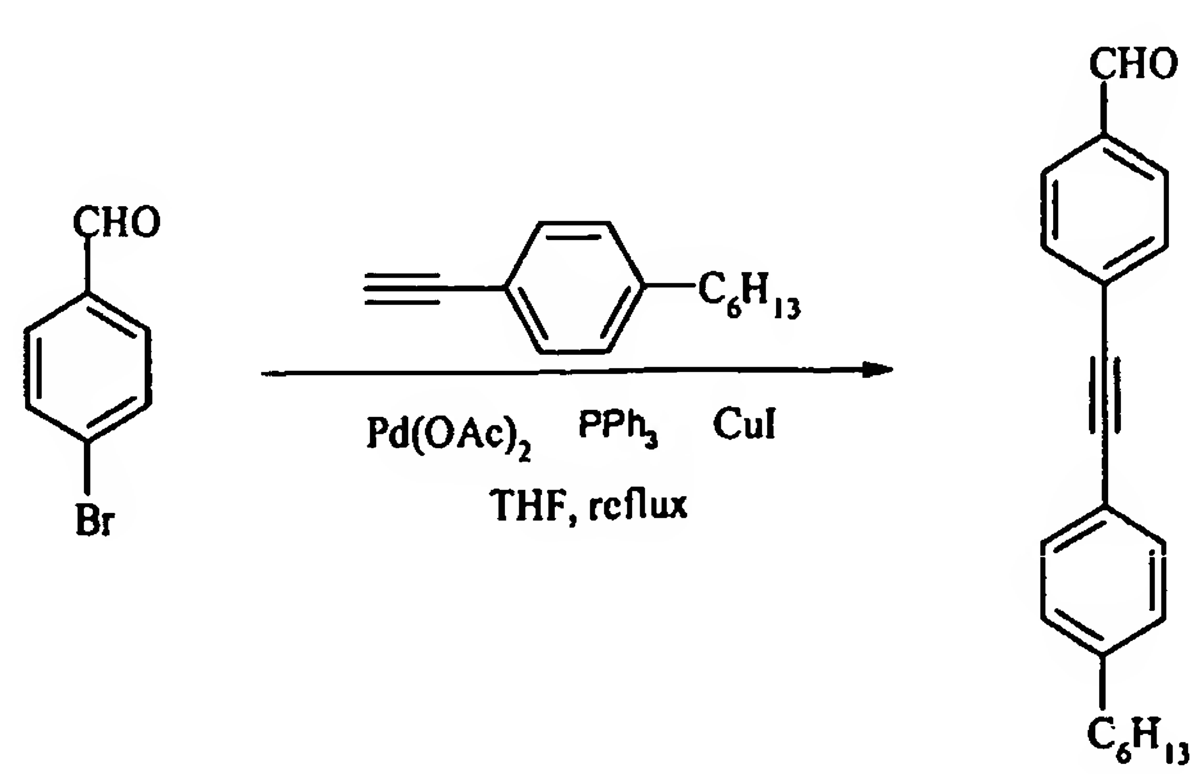
A Japanese application (JP 07138196, published on 30 May 1995), for instance, describes the following specific method. The method involves the use of a Palladium catalyst in two separate steps.

Scheme 1



A further application related to para-phenyl alkynyl benzaldehyde, is PCT/EPO3/00808 (priority date: 29 January 2002). It also implies the use of a palladium catalyst and discloses the following specific pathway for synthesizing para-phenyl alkynyl benzaldehyde:

Scheme 2



The methods used in the art imply the use of costly Palladium catalysts. Furthermore, the use of Palladium catalysts causes Palladium contamination and frequently, formation of undesired by-products. The present invention provides a new method that does not require the use of Palladium catalysts.

Description of the invention

The present invention allows to overcome the above said problems by a synthesis that involves four steps and moreover uses, as starting compounds, compounds that may be easily synthesized or are commercially available.

The following paragraphs provide definitions of the various chemical moieties that make up the compounds according to the invention and are intended to apply uniformly throughout the specification and claims unless an otherwise expressly set out definition provides a broader definition.

"C_1-C_{12} -alkyl" refers to alkyl groups having 1 to 12 carbon atoms. This term is exemplified by groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, *tert*-butyl, n-hexyl, heptyl, octyl, nonyl and the like.

"C_1-C_{12}-alkyl aryl" refers to C_1-C_{12}-alkyl groups having an aryl substituent, including benzyl, phenethyl and the like.

"Aryl" refers to an unsaturated aromatic carbocyclic group of from 6 to 14 carbon atoms having a single ring (*e.g.*, phenyl) or multiple condensed rings (*e.g.*, naphthyl). Preferred aryl include phenyl, naphthyl, phenantrenyl and the like.

"Heteroaryl" refers to a monocyclic heteroaromatic, or a bicyclic or a tricyclic fused-ring heteroaromatic group. Particular examples of heteroaromatic groups include optionally substituted pyridyl, pyrrolyl, furyl, thienyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadia-zolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl,1,3,4-triazinyl, 1,2,3-triazinyl, benzofuryl, [2,3-dihydro]benzofuryl, isobenzofuryl, benzothienyl, benzotriazolyl, isobenzothienyl, indolyl, isoindolyl, 3H-indolyl, benzimidazolyl, imidazo[1,2-a]pyridyl, benzothiazolyl, benzoxa-zolyl, quinolizinyl, quinazolinyl, pthalazinyl, quinoxalinyl,

cinnolinyl, napthyridinyl, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]pyridyl, quinolyl, isoquinolyl, tetrazolyl, 5,6,7,8-tetrahydroquinolyl, 5,6,7,8-tetrahydroisoquinolyl, purinyl, pteridinyl, carbazolyl, xanthenyl or benzoquinolyl.

"Halogen" refers to fluoro, chloro, bromo and iodo atoms.

"C_1-C_{12}-alkyl heteroaryl" refers to C_1-C_{12}-alkyl groups having a heteroaryl substituent, including 2-furylmethyl, 2-thienylmethyl, 2-(1H-indol-3-yl)ethyl and the like.

"C_2-C_{12}-alkenyl" refers to alkenyl groups preferably having from 2 to 12 carbon atoms and having at least 1 or 2 sites of alkenyl unsaturation. Such alkenyl groups include ethenyl ($-CH=CH_2$), n-2-propenyl (allyl, $-CH_2CH=CH_2$) and the like.

"C_2-C_{12}-alkenyl aryl" refers to C_2-C_{12}-alkenyl groups having an aryl substituent, including 2-phenylvinyl and the like.

"C_2-C_{12}-alkenyl heteroaryl" refers to C_2-C_{12}-alkenyl groups having a heteroaryl substituent, including 2-(3-pyridinyl)vinyl and the like.

"C_2-C_{12}-alkynyl" refers to alkynyl groups preferably having from 2 to 12 carbon atoms and having at least 1-2 sites of alkynyl unsaturation, preferred alkynyl groups include ethynyl ($-C\equiv CH$), propargyl ($-CH_2C\equiv CH$), and the like.

"C_2-C_{12}-alkynyl aryl" refers to C_2-C_{12}-alkynyl groups having an aryl substituent, including phenylethynyl and the like.

"C_2-C_{12}-alkynyl heteroaryl" refers to C_2-C_{12}-alkynyl groups having a heteroaryl substituent, including 2-thienylethynyl and the like.

"C_3-C_8-cycloalkyl" refers to a saturated carbocyclic group of from 3 to 8 carbon atoms having a single ring (*e.g.*, cyclohexyl) or multiple condensed rings (*e.g.*, norbornyl). Preferred cycloalkyl include cyclopentyl, cyclohexyl, norbornyl and the like.

"C_1-C_{12}-alkyl cycloalkyl" refers to C_1-C_{12}-alkyl groups having a cycloalkyl substituent, including cyclohexylmethyl, cyclopentylpropyl, and the like.

"Alkoxy" refers to the group –O-R where R includes "C_1-C_6-alkyl", "C_2-C_6-alkenyl", "C_2-C_6-alkynyl", "C_3-C_8-cycloalkyl", "heterocycloalkyl", "aryl", "heteroaryl", "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl", "C_2-C_6-alkenyl aryl", "C_2-C_6-alkenyl heteroaryl", "C_2-C_6-alkynyl aryl", "C_2-C_6-alkynylheteroaryl", "C_1-C_6-alkyl cycloalkyl", "C_1-C_6-alkyl heterocycloalkyl".

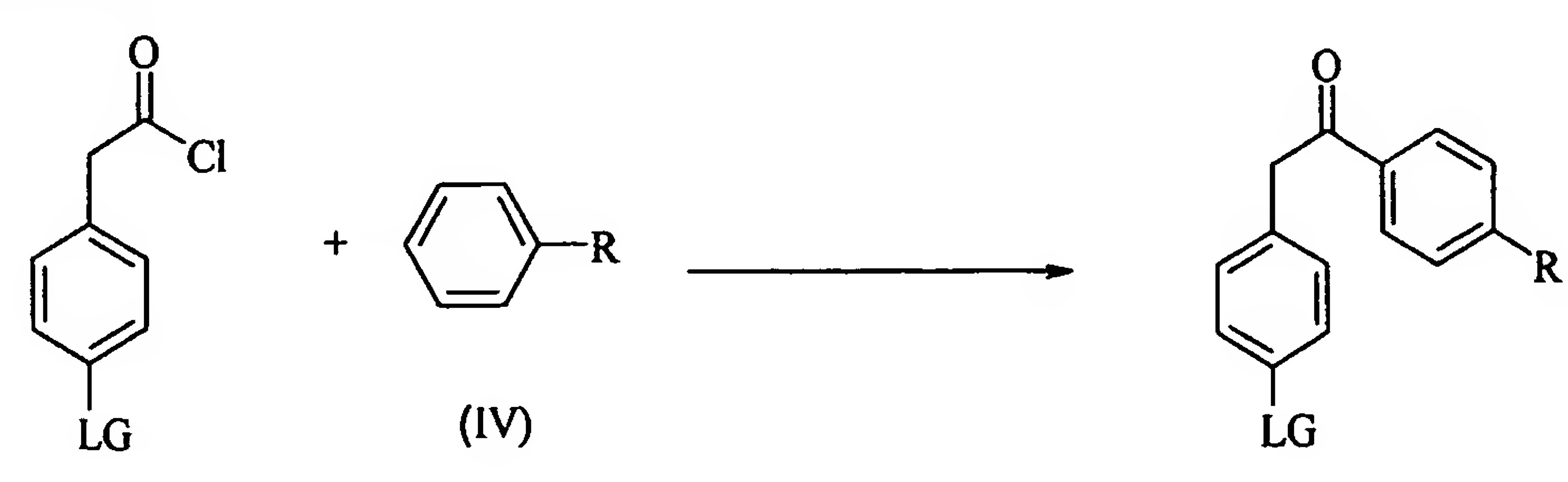
The method, according to the present invention, comprises or consists of the following steps 1 to 4 :

According to the invention the building block of formula (I) can be prepared starting either from compound of general formula (II) or from compound of general formula (III) wherein LG is a suitable leaving group. Compounds (II) and (III) (e.g. bromide, chloride, iodide) are commercially available or may be prepared according to known techniques.

Step 1 : An acyl chloride (III) is coupled with a substituted benzene of formula (IV), wherein R is selected from the group consisting of C_1-C_{12}–alkyl, C_1-C_{12}-alkyl aryl, C_1-C_{12}-alkyl heteroaryl, C_2-C_{12}-alkenyl, C_2-C_{12}-alkenyl aryl, C_2-C_{12}-alkenyl heteroaryl, C_2-C_{12}-alkynyl, C_2-C_{12}-alkynyl aryl, C_2-C_{12}-alkynyl heteroaryl, C_3-C_8-cycloalkyl, C_1-C_{12}–alkoxy, aryl, heteroaryl or a halide, thus yielding a ketone of formula (V).

LG is a suitable leaving group like a halide (Br, Cl, I).

Scheme 3

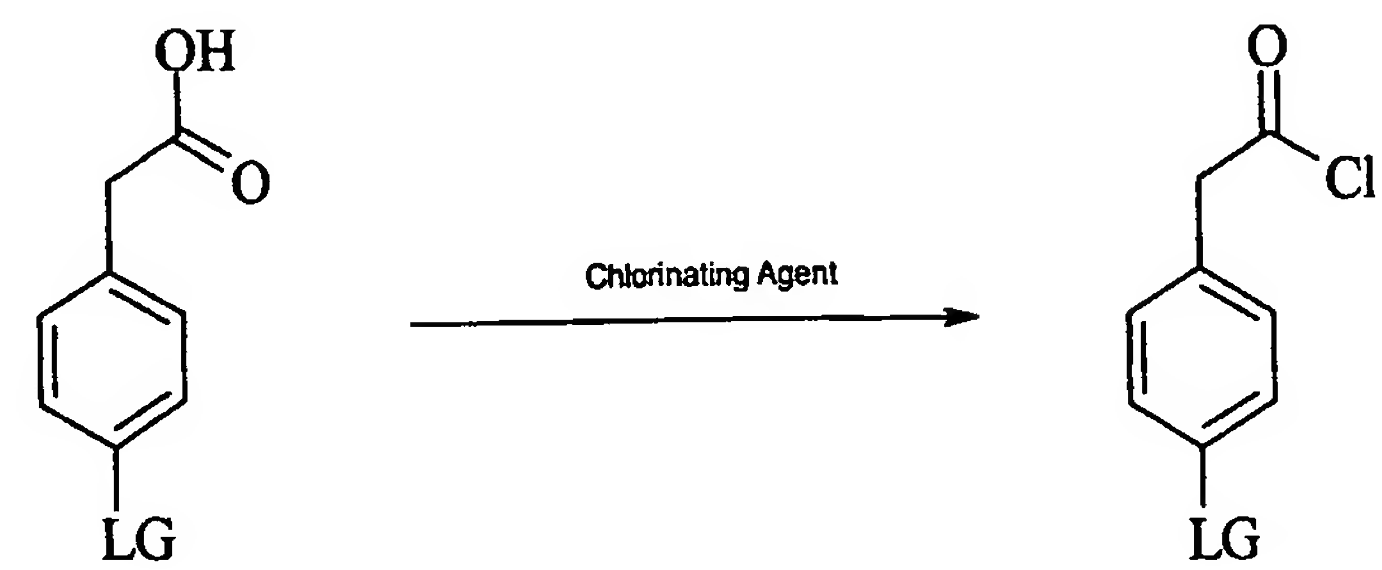


(III) (V)

Preferably, the reaction is performed in the presence of a Lewis acid (for example $FeCl_3$, $AlCl_3$) in a range of temperature from room temperature to 50 °C, typically for a period of about 5 hours.

The acyl chloride starting compound (III) in Scheme 3 is typically obtained by reaction of the acid (II) with a suitable chlorinating agent, e.g. thionyl chloride, oxalyl chloride, PCl_3 or PCl_5

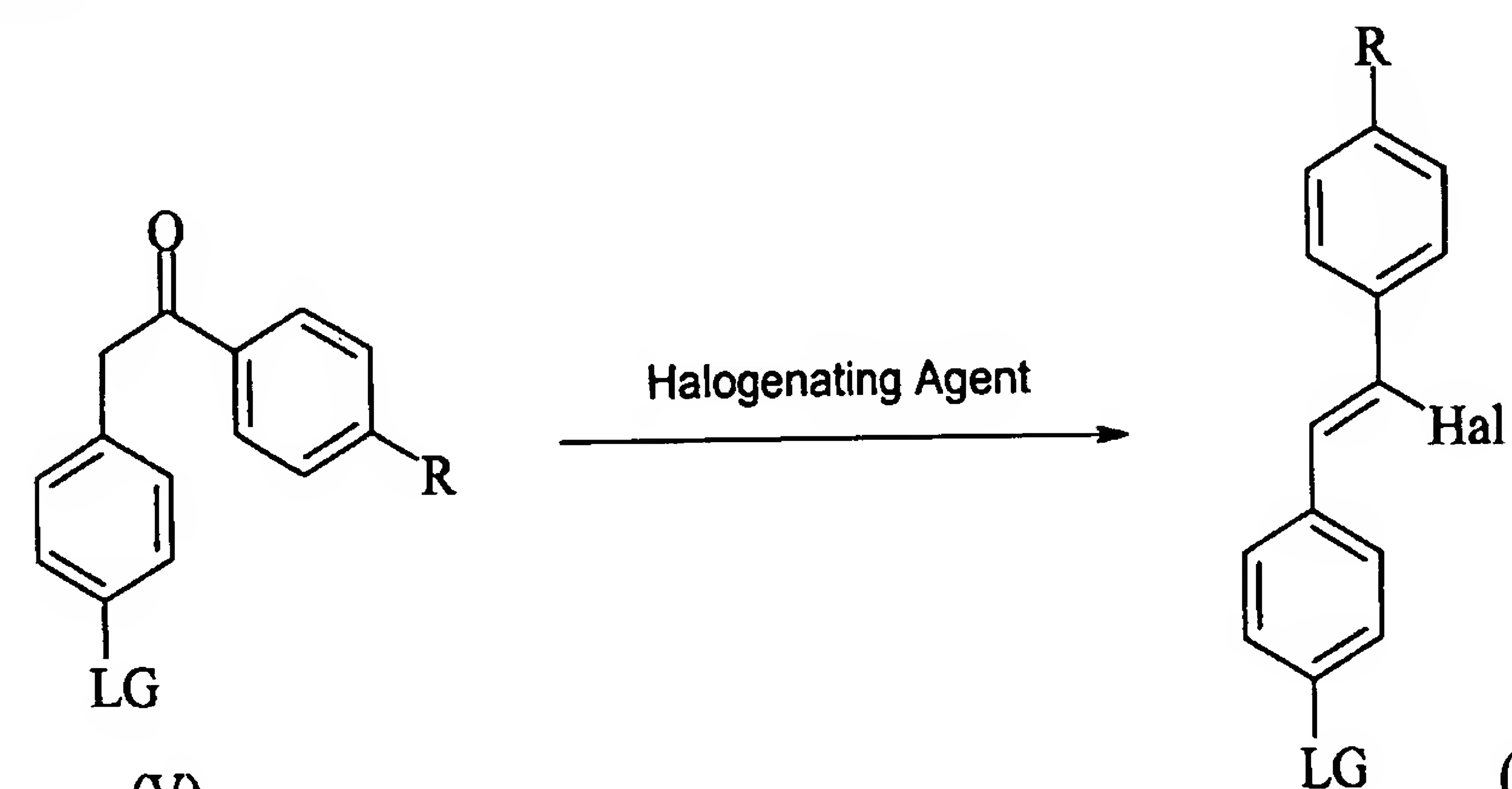
Scheme 4



(II) (III)

Step 2 : Then, the compound of formula (V) is transformed into compound (VI) using a suitable halogenating agent including acyl chlorides, e.g. acetyl chloride, bromide.

Scheme 5



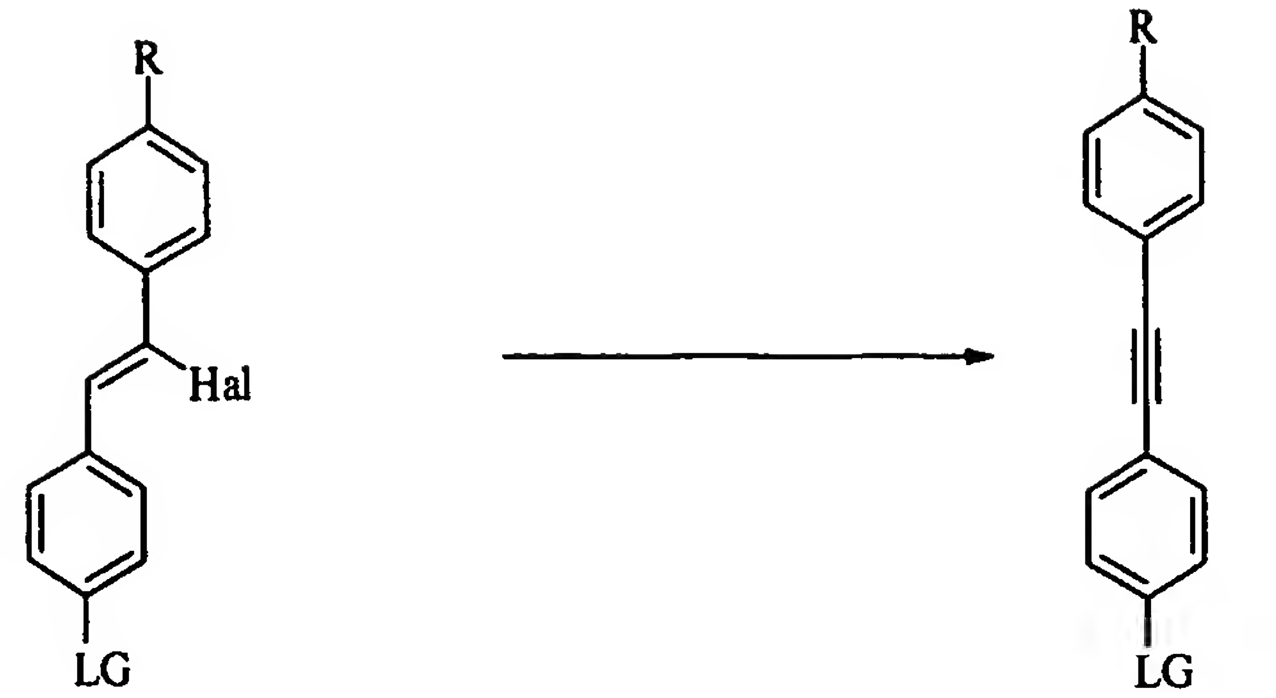
(V) (VI)

Hal is Br, Cl.

Preferably, the reaction is performed with an acyl chloride in an acidic organic solvent (TFA or methane sulfonic acid) preferentially TFA at room temperature, typically for a period of 40 hours.

Step 3 : The compound (VI) is then transformed into compound (VII) by eliminating HCl, preferably in an alkaline medium (dehydrohalogenation).

Scheme 6



(VI) (VII)

Preferably the reaction is performed in an organic solvent (for example a mixture of dioxane and methanol), typically in presence of a base (preferred bases include NaOH and KOH), at a temperature of 80 °C, typically for a period of 20 hours.

Step 4 : In a final step, a compound of formula (VII) is reacted with a formylating agent (VIII) to give compound (I). In one embodiment, a compound of formula (VII), wherein LG is a halide, is first transformed into an activated species, e.g. an organometallic derivative, such as organo-magnesium or organo-lithium using magnesium or butyl lithium respectively. The activated species, e.g. the organo-metallic derivative, is then transformed into the aldehyde of formula (I) by reaction with a formylating agent such as DMF, 1-formyl-piperidine, 1-formyl piperazine, N-methyl-N-(2-pyridyl) formamide, N-methyl formanilide, Weinreb formamide (e.g : N-methoxy-N-methylformamide). The two steps protocol can be performed in one pot or successively.

In one embodiment, a compound (VII) is provided; Mg in an organic solvent such as THF as well as 1-formyl-piperidine are added in order to perform a one-pot reaction.

In a further embodiment compound (VII) is provided; n-butyl lithium in THF as well as DMF as formylating agent are added in order to perform a one-pot reaction.

Scheme 7

(VII) (I)

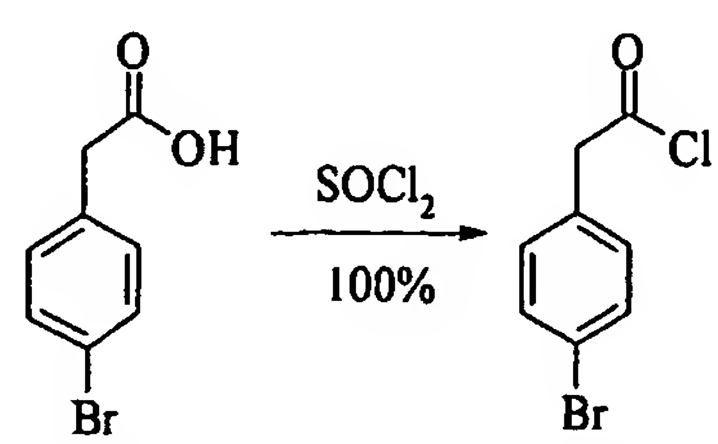
In a specific embodiment, the novel method allows the preparation of compounds according to formula (I), wherein R is C_1-C_6 –alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, *tert*-butyl, n-hexyl, moiety).

The new synthetic approach for preparing the compounds of formula (I) has the advantage that it does not involve the use of palladium.

The present invention shall be illustrated by means of the following examples. It will be appreciated that where typical or preferred experimental conditions (i.e., reaction temperatures, time, moles of reagents, solvents, etc.) are given, other experimental conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvents used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

Example 1: Preparation of 4-(4-methoxy-phenylethynyl)-benzaldehyde

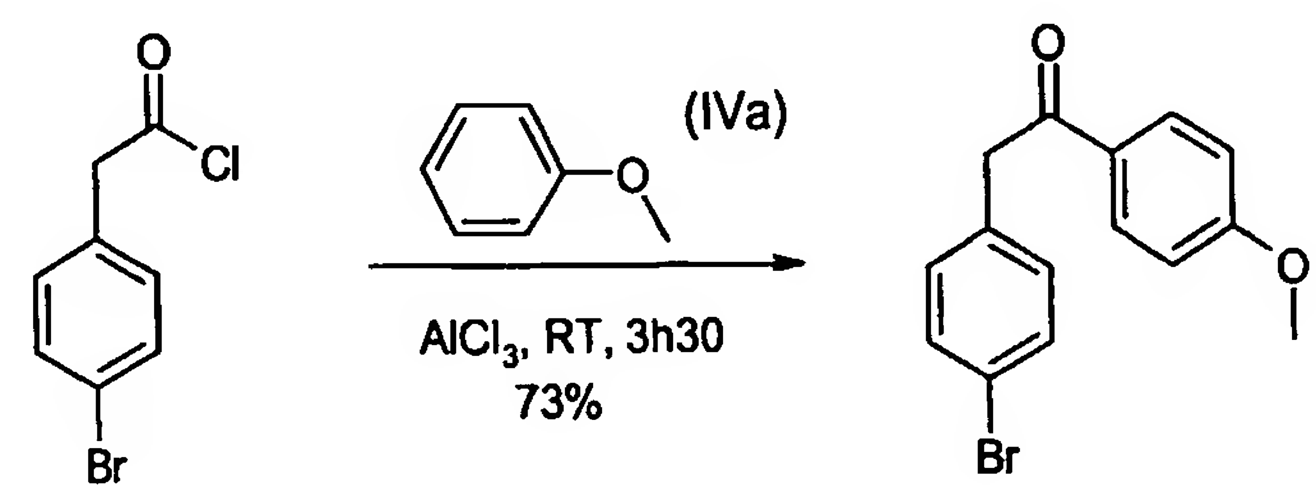
a) Synthesis of (4-bromo-phenyl)-acetyl chloride (IIIa)



(IIa) (IIIa)

In a 1L flask, topped with an HCl trap, $SOCl_2$ (495ml; 3vols) was added into (4-bromo-phenyl)-acetic acid (IIa) (165g; 767.28mmol). The reaction mixture was stirred at 60°C for 3h. Then, it was concentrated under vacuum and co-evaporated with toluene (100mL). The resulting light brown oil was dried under vacuum for 48h protected from the light using an aluminum foil. The title compound (m=178.20g) was obtained as oil in a yield of 99.5%.

b) Step 1: Synthesis of 2-(4-bromophenyl)-1-(4-methoxyphenyl) ethanone (Va)



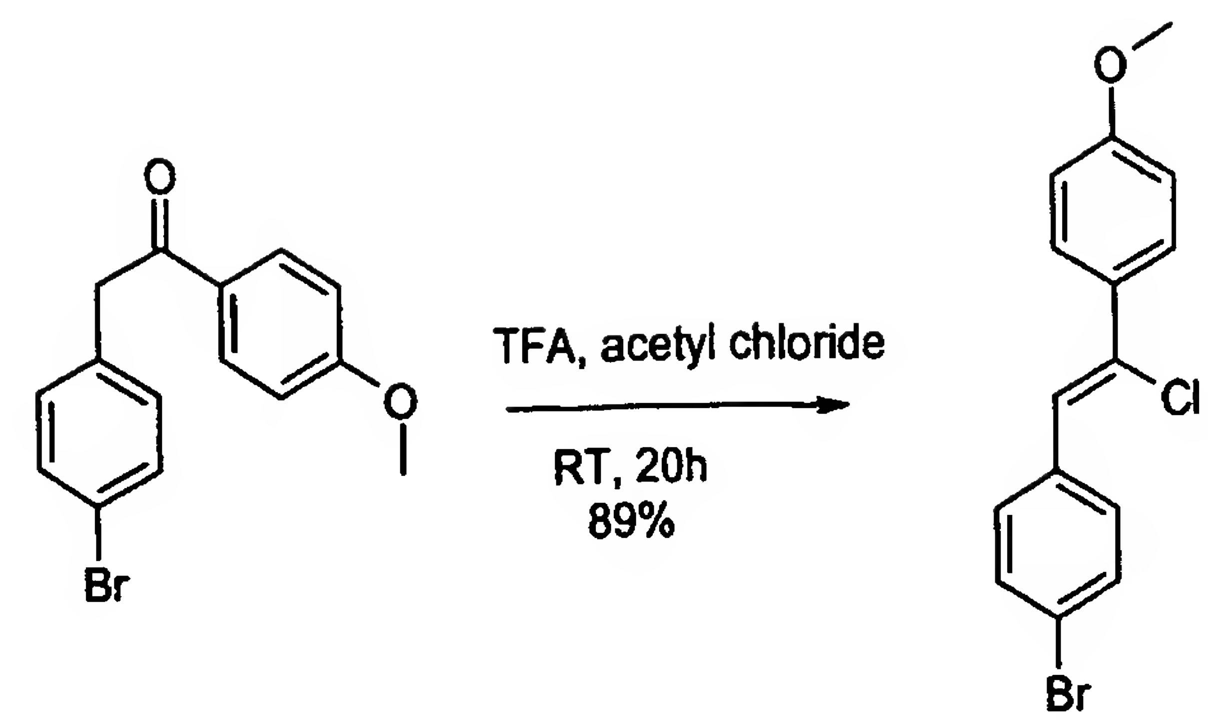
(IIIa) (Va)

To a 50mL three-necked flask containing $AlCl_3$ (4.406g; 33.05mmol) under N_2, anisole (IVa) (4.467g; 41.31mmol) was added in one portion at RT. The reaction was exothermic. To this suspension (4-bromo-phenyl)-acetyl chloride (IIIa) (6.430g; 27.54mmol) was added drop wise keeping temperature below 20°C. Then the resulting red suspension was stirred at RT for 3h30. The red thick solution was poured under stirring into a mixture of ice and 1N HCl (100mL), then the resulting white solid was filtered, and washed with water. The solid was washed with pentane (3x30mL) and dried under vacuum at RT to give a white powder (m=8.51g). Purification was performed by crystallization from acetone (30ml) to give the title compound as a white powder (m=6.113g) in a 73% yield.

1H-NMR (CDCl3=7.26ppm) : 7.97 (d, J=8.85 Hz, 2H), 7.44 (d, J=8.28 Hz, 2H), 7.13 (d, J=8.28 Hz, 2H), 6.93 (d, J=8.85 Hz, 2H), 4.18 (s, 2H), 3.86 (s, 3H)

Melting point: 142°C

c) Step 2: Synthesis of 4-[(Z)-2-(4-bromophenyl)-1-chlorovinyl] phenyl methyl ether (VIa)

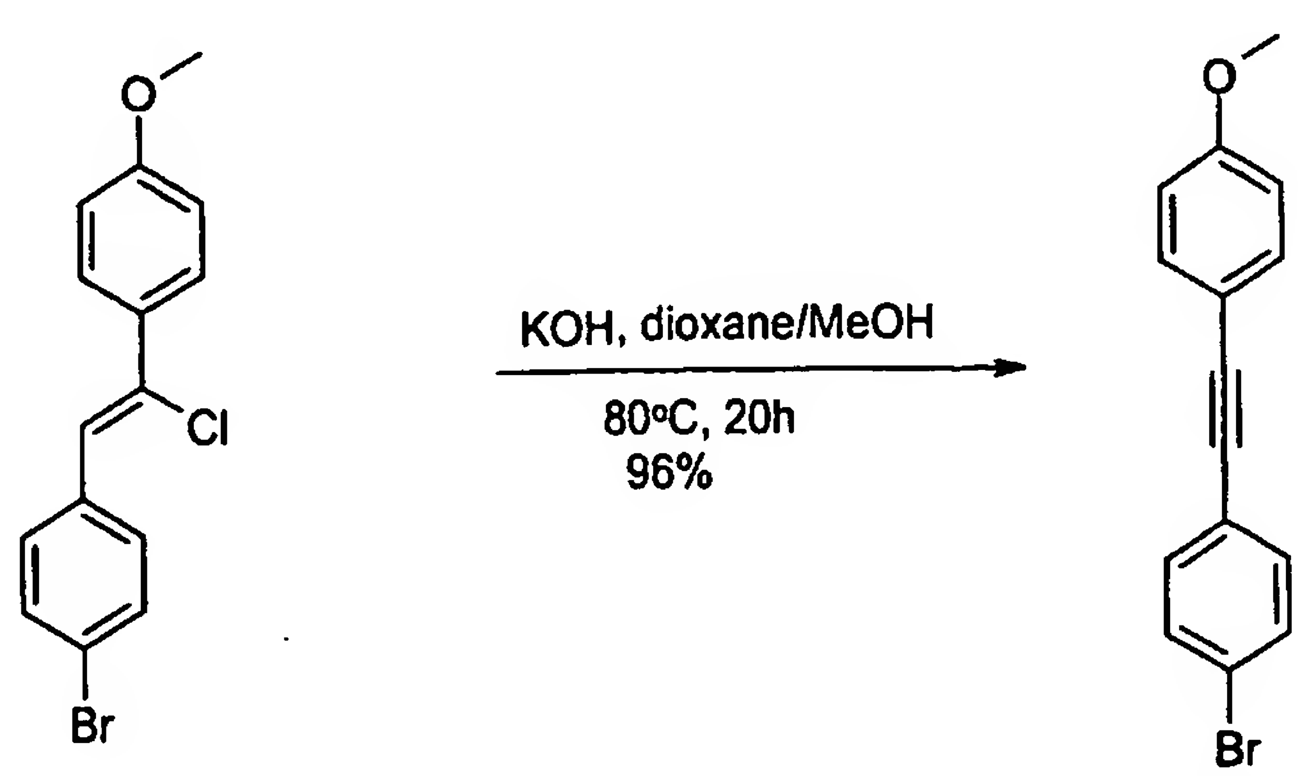


(Va) (VIa)

In a 100mL flask, TFA (15mL; 197.30mmol) and acetyl chloride (11.17mL; 157.81mmol) were added in one portion into 2-(4-bromophenyl)-1-(4-methoxyphenyl) ethanone (Va) (6.02g; 19.73mmol) at RT. Pink reaction mixture was vigorously stirred at RT for 20h. The resulting brown suspension was cooled to 0°C, filtered and washed with TFA (2 x 10mL). The off-white solid was dried under vacuum at 30°C. The title compound (m= 5.688g) was obtained in a 89% yield. Melting point: 97°C

1H-NMR (CDCl3=7.26ppm) : 7.60 (t, J=8.94 Hz, 4H), 7.50 (d, J=8.66 Hz, 2H), 6.92 (d, J=8.85 Hz, 2H), 6.89 (s, 1H), 3.85 (s, 3H)

d) Step 3: Synthesis of 4-[(4-bromophenyl) ethynyl] phenyl methyl ether (VIIa)



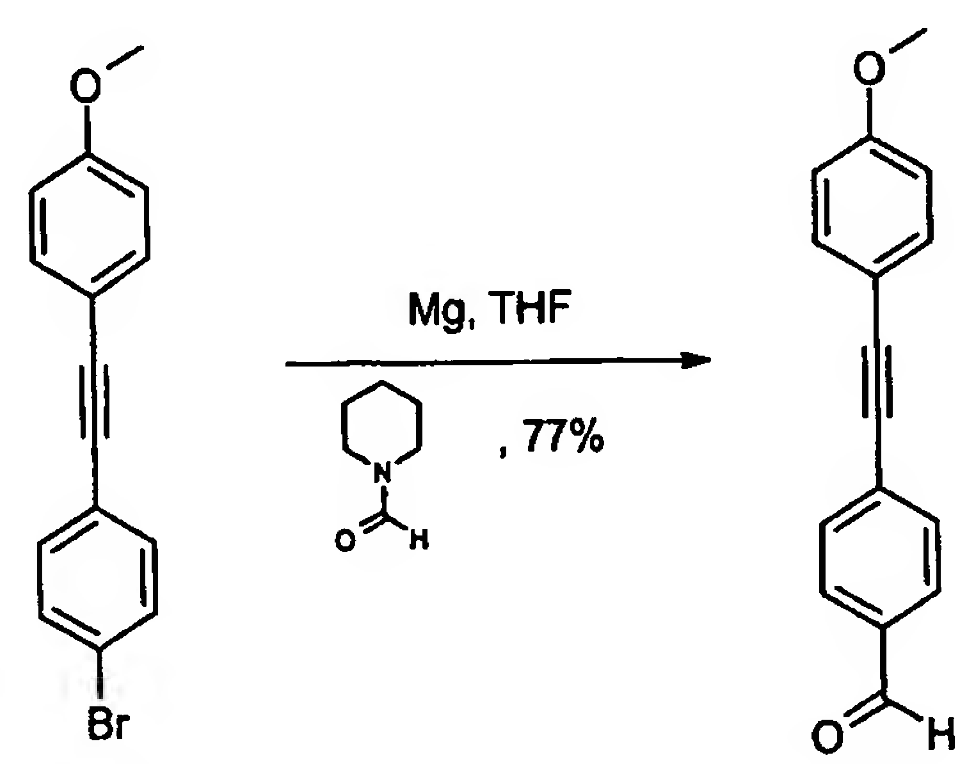
(VIa) (VIIa)

To a 100mL flask containing a solution of 4-[(Z)-2-(4-bromophenyl)-1-chlorovinyl] phenyl methyl ether (VIa) (5.613g; 17.34mmol) in 1,4-dioxane (28mL; 5vols) and MeOH (8mL; 1.4vols), KOH (1.946g; 34.69mmol) was added in one portion. Reaction

mixture was stirred at 80°C overnight. Reaction mixture was taken up in water (200mL) and the resulting suspension was filtered and washed with water to give a white solid. Drying under vacuum at 33°C overnight gave the title compound (m=4.786g) in a 96% yield. Melting point: 152°C

1H-NMR (CDCl3=7.26ppm) : 7.40 (d, J=2.26 Hz, 2H), 7.37 (d, J=2.26 Hz, 2H), 7.28 (d, J=8.47 Hz, 2H), 6.80 (d, J=8.85 Hz, 2H), 3.75 (s, 3H)

e) Step 4: Synthesis of 4-[(4-methoxyphenyl) ethynyl] benzaldehyde (Ia)



(VIIa) (Ia)

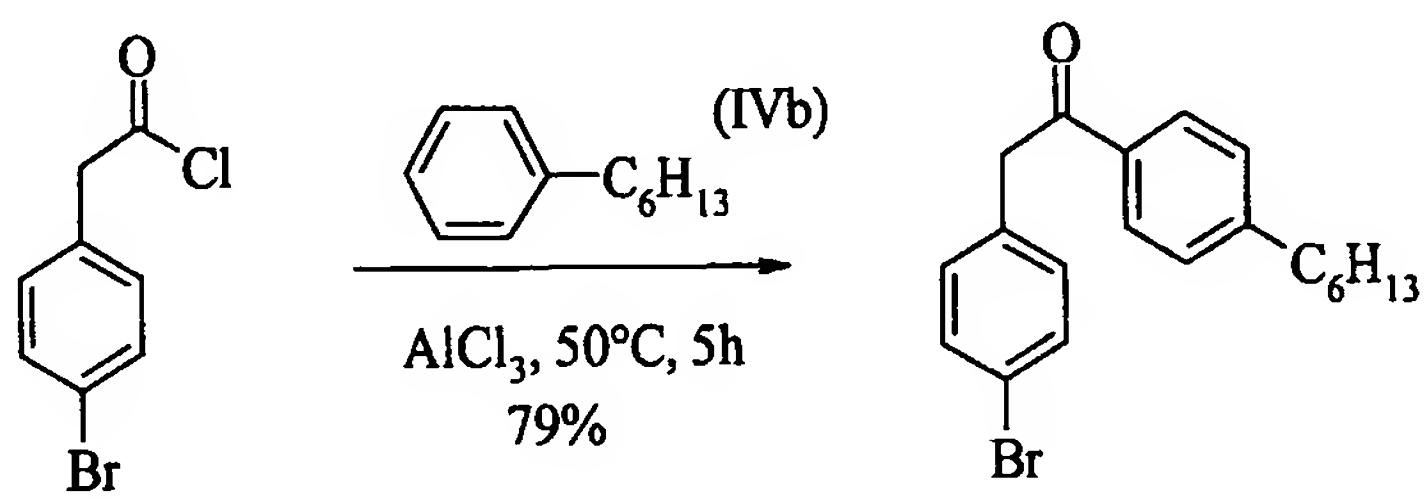
To a dry 100mL three-necked flask containing magnesium turnings (0.447g; 18.38mmol) in dry THF (8mL), a small portion of 4-[(4-bromophenyl) ethynyl] phenyl methyl ether (VIIa) (0.300g; 1.044mmol) was added in one portion, at reflux under a flow of N_2. N_2 flow and stirring were stopped. The reaction mixture was heated at reflux for 5 minutes then iodine crystals were added, while reflux is maintained to start the reaction. A solution of remaining amount of 4-[(4-bromophenyl) ethynyl] phenyl methyl ether (VIIa) (4.5g; 15.67mmol) in dry THF (30mL) was added drop wise into the reaction mixture while keeping gentle reflux. Reflux was maintained for 15minutes then temperature was allowed to cool to RT under stirring for 1h. The reaction mixture was cooled to 3°C and a solution of dry 1-formyl-piperidine (2.8mL; 25.07mmol) in dry THF (10mL) was added drop wise maintaining temperature at 5°C. The reaction mixture was then allowed to warm to RT and it was stirred overnight. The reaction mixture was cooled to 18°C and 3N HCl (30mL) was added. Water was added (50mL) and extraction was performed with MTBE (50mL x 3). Organic phase was washed successively with water (50mL x 2), saturated solution of $NaHCO_3$ (50mL x 1) and

brine (50mL x 1). It was then dried over $MgSO_4$, filtered and concentrated to give a yellow solid. It was taken up in Pet ether (40mL) and left at 4°C.After 16h the suspension was filtered and washed with Pet ether (2 x 30mL) to give after drying under vacuum a clear yellow solid. The title compound was obtained (m = 3.06g) in a 77% yield. Melting point: 106 °C

1H-NMR (CDCl3=7.26ppm) : 10.0 (s, 1H), 7.85 (d, J=8.28 Hz, 2H), 7.64 (d, J=8.28 Hz, 2H), 7.49 (d, J=8.85 Hz, 2H), 6.90 (d, J=8.85 Hz, 2H), 3.84 (s, 3H)

Example 2 : Preparation of 4-(4-hexyl-phenylethynyl)-benzaldehyde

a) Step 1 : Synthesis of 2-(4-bromo-phenyl)-1-(4-hexyl-phenyl)-ethanone (Vb)

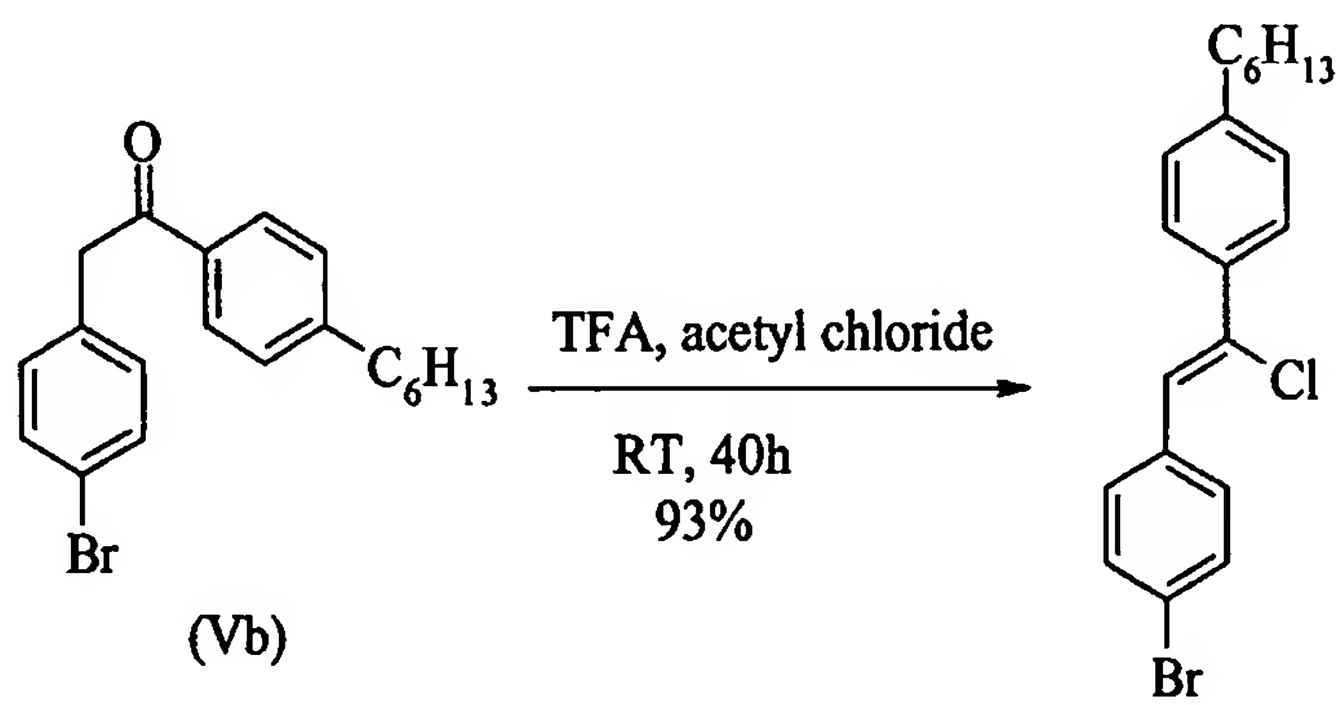


(IIIa) (Vb)

To a 2L three-necked flask, set up with a mechanical stirring, containing $AlCl_3$ (85.661g; 642.42mmol) under N_2, 4-hexylbenzene (IVb) (104.25 g; 642.42mmol) was added in one portion at room temperature. To this resulting orange suspension (4-bromo-phenyl)-acetyl chloride (IIIa) (125.000 g; 535.35mmol) was added drop wise during 45 minutes without cooling. Then reaction mixture was stirred for 3h until temperature cooled down to room temperature, time when no more foaming was observed. The deep brown mixture was then stirred at room temperature overnight. The black thick solution was poured under stirring into a mixture of ice and 1N HCl (800mL), then the resulting white-orange solid was filtered, and washed successively with water, saturated solution of $NaHCO_3$ and finally with water until pH of the filtrate was 7. The solid was washed with heptane (3x200mL) and dried under vacuum at room temperature to give the title compound as a white powder (m=151.15 g) in a 79% yield. Melting point: 108°C

1H-NMR (CDCl3=7.26ppm) : 7.91 (d, J=8.28 Hz, 2H), 7.44 (d, J=8.28 Hz, 2H), 7.26 (d, J=8.28 Hz, 2H), 7.13 (d, J=8.47 Hz, 2H), 4.21 (s, 2H), 2.65 (t, J=7.81 Hz, 2H), 1.62 (quint, J=7.53 Hz, 2H), 1.43-1.22(br m, 6H), 0.88 (t, J=6.87 Hz, 3H)

b) Step 2 : Synthesis of 1-bromo-4- [(Z)-2-chloro-2- (4-hexylphenyl) vinyl] benzene (VIb)

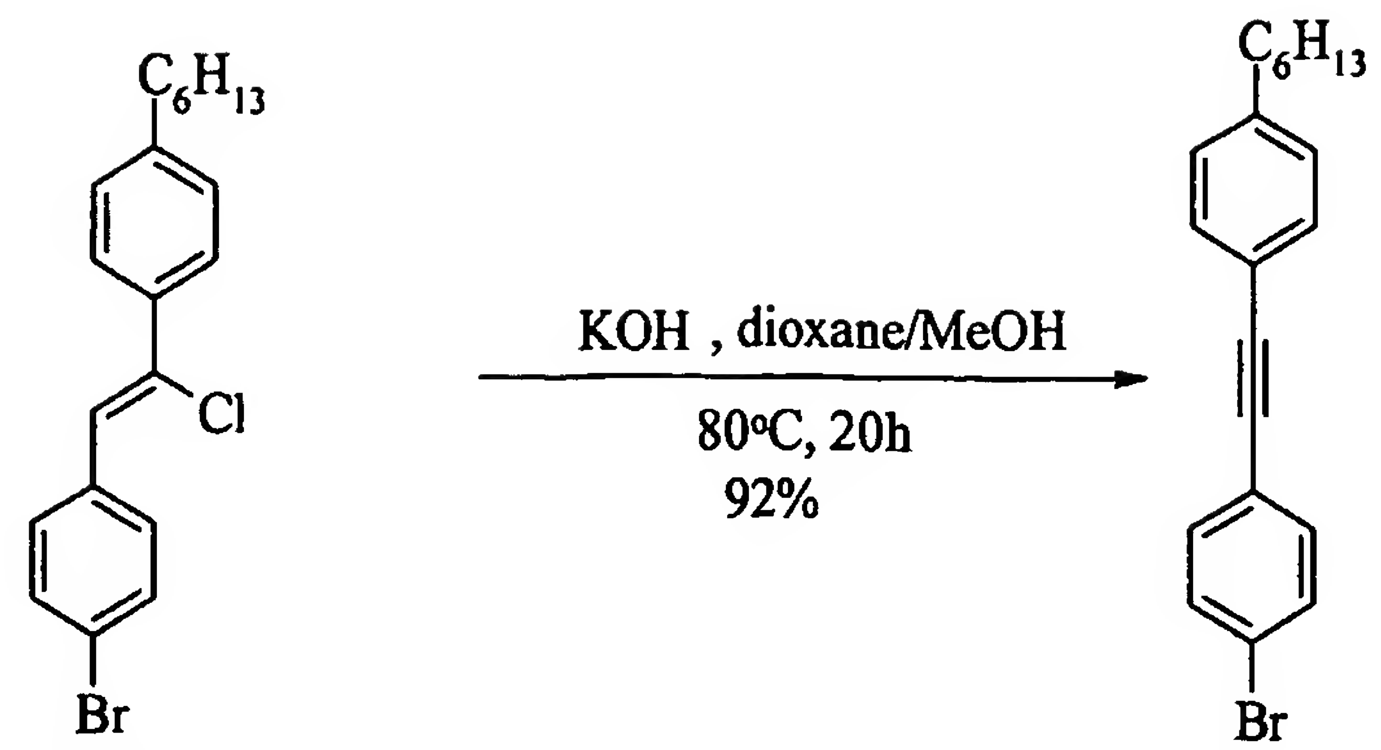


(Vb) (VIb)

In a 2L flask, TFA (464.17mL; 6065.60mmol) and acetyl chloride (344.71mL; 4852.42mmol) were added in one portion into 2-(4-bromo-phenyl)-1-p-tolyl-ethanone (Vb) (217.940 g; 606.56mmol) at room temperature. Reaction mixture was vigorously stirred at room temperature for 40h. The resulting suspension was cooled to 0°C, filtered and washed with TFA (100mL). The white solid was dried under vacuum at 30°C . The title compound (m= 209.79g) was obtained in a 93% yield. Melting point: 52°C

1H-NMR (CDCl3=7.26ppm) : 7.61 (d, J=3.01 Hz, 2H), 7.58 (d, J=3.01 Hz, 2H), 7.51 (d, J=8.66 Hz, 2H), 7.21 (d, J=8.47 Hz, 2H), 6.96 (s, 1H), 2.63 (t, J=7.81 Hz, 2H), 1.70-1.53(br m, 2H), 1.45-1.20(br m, 6H), 0.89 (t, J=6.87 Hz, 3H)

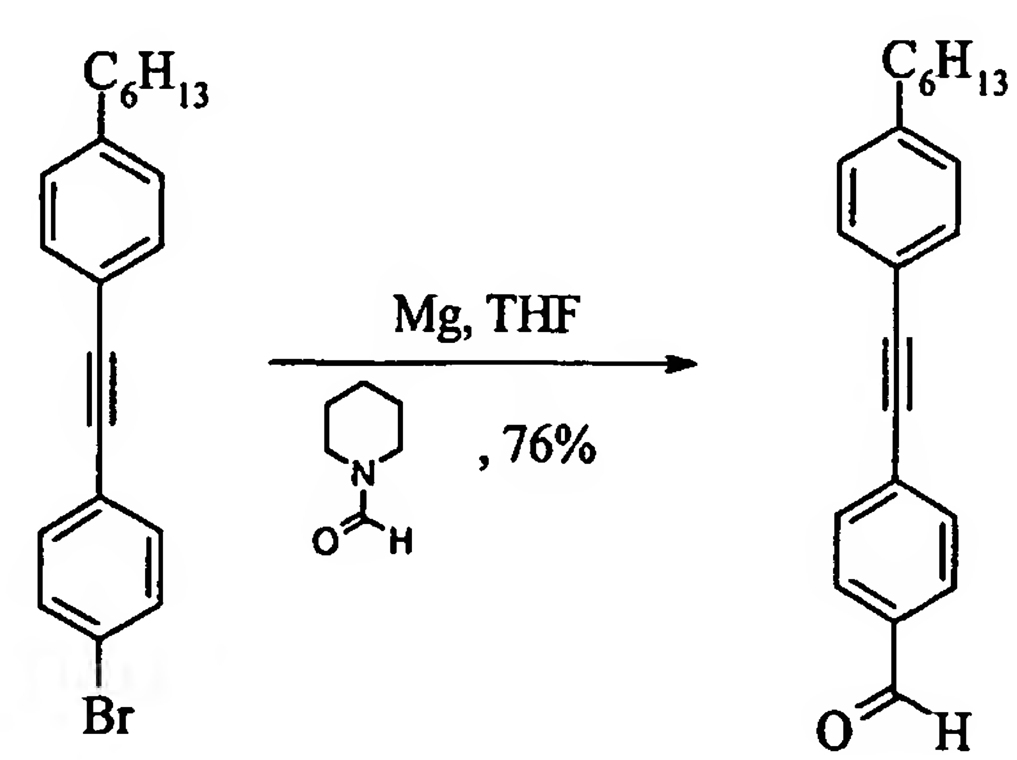
c) Step 3 : Synthesis of 1-bromo-4- [(4-hexylphenyl) ethynyl] benzene (VIIb)



(VIb) (VIIb)

To a 2L flask containing a solution of 1-bromo-4-[(Z)-2-chloro-2-(4-hexylphenyl) vinyl] benzene (VIb) (209.79g; 555.37mmol) in 1,4-dioxane (1000mL; 4.8vols) and MeOH (300mL; 1.4vols), KOH (62.32g; 1110.73mmol) was added in one portion. Reaction mixture was stirred at 80°C overnight. Volume was reduced under vacuum to 200mL and the residue was taken up in water (2000mL). The resulting suspension was filtered and washed with water to give a clear beige solid. Drying under vacuum at 33°C overnight gave the title compound (m=173.34g) in a 92% yield. Melting point : 67°C
1H-NMR (CDCl3=7.26ppm): 7.47 (d, J=8.66 Hz, 2H), 7.43 (d, J=8.10 Hz, 2H), 7.37 (d, J=8.28 Hz, 2H), 7.16 (d, J=8.10 Hz, 2H), 2.61 (t, J=7.81 Hz, 2H), 1.59 (quint, J=7.48 Hz, 2H), 1.42-1.21(br s, 6H), 0.88 (t, J=6.31 Hz, 3H)

d) <u>Step 4 : Synthesis of 4-(4-hexyl-phenylethynyl)-benzaldehyde (Ib)</u>



(VIIb) (Ib)

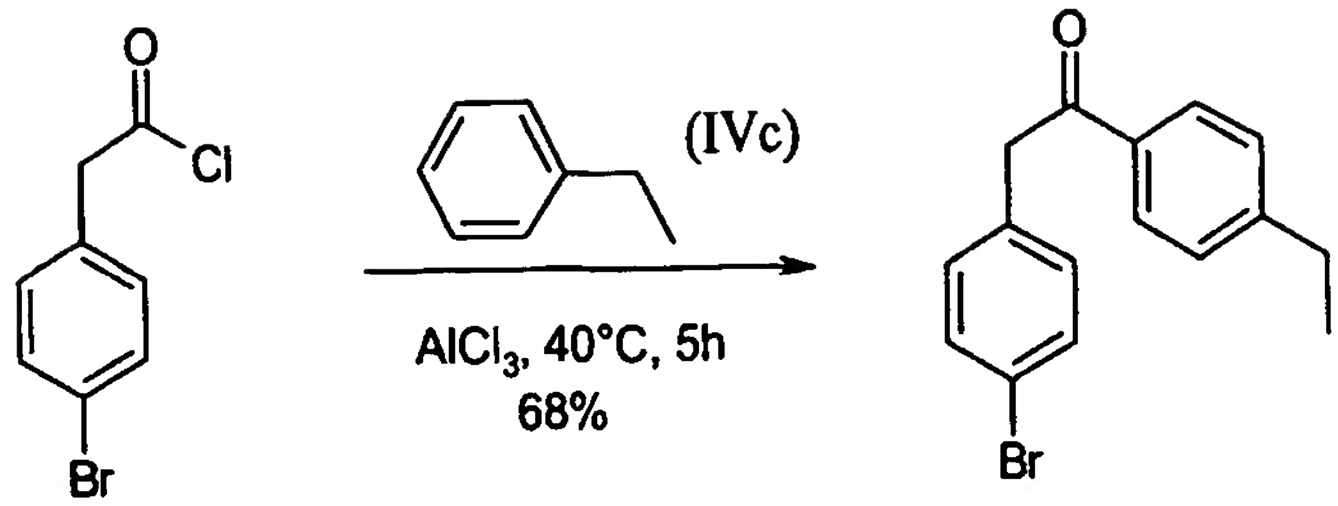
To a dry 2L three-necked flask under a flow of N_2 containing magnesium turnings (13.579g; 558.69mmol) in dry THF (165mL) at reflux (temperature of bath oil of 85°C),

an activating, small amount of 1-bromo-4-[(4-hexylphenyl) ethynyl] benzene (VIIb) (10.400g; 30.474mmol) was added in one portion. N_2 flow and stirring were stopped. Reaction mixture was heated at reflux for 5 minutes, then several iodine crystals were added keeping vigorous reflux to start the reaction. The reaction mixture went colorless after 5 minutes and reaction mixture turned black-green after an additional minute. A solution of the remaining amount of 1-bromo-4-[(4-hexylphenyl) ethynyl] benzene (VIIb) (162.94g; 477.42mmol) in dry THF (360mL) was added drop wise over 40 minutes into the reaction mixture while keeping gentle reflux. Reflux was maintained for 20minutes then temperature was allowed to cool to room temperature under stirring for 2h30. The reaction mixture was cooled to 3°C and a solution of dry 1-formyl-piperidine (84.60mL; 761.85mmol) in dry THF (360mL) was added drop wise over 1 hour maintaining temperature at 5°C (maximum temperature: 7.3°C). The reaction mixture was then allowed to warm to room temperature and it was stirred overnight. The reaction mixture was cooled to 18°C and 3N HCl (300mL) was added until the solution was acidic (pH=1). Water was added (500mL) and extraction was performed with MTBE (500mL x 3). Organic phase was washed successively with water (500mL x 2), saturated solution of $NaHCO_3$ (500mL x 1) and brine (500mL x 1). It was then dried over $MgSO_4$, filtered and concentrated to give an orange solid. It was taken up in Pet ether (400mL) and left at 4°C. After 16h the suspension was filtered and washed with Pet ether (2 x 300mL) to give after drying under vacuum the first crop m= 105.76g. Filtrate was concentrated and taken up in Pet ether (100mL). The resulting solid was washed with Pet ether (2 x 100mL), and dried to give the second crop m=6.0g. The title compound was obtained as a white solid (m= 111.76g) in a 76% yield. Melting point: 80°C

1H-NMR (DMSO=2.49ppm): 10.0 (s, 1H), 7.93 (d, J=8.28 Hz, 2H), 7.74 (d, J=8.28 Hz, 2H), 7.5 (d, J=8.28 Hz, 2H), 7.26 (d, J=8.28 Hz, 2H), 2.60 (t, J=7.81 Hz, 2H), 1.56 (quint, J=7.44 Hz, 2H), 1.36-1.16 (br s, 6H), 0.84 (t, J=6.78 Hz, 3H)

<u>Example 3: Preparation of 4-(4-ethyl-phenylethynyl)-benzaldehyde</u>

a) <u>Step 1: Synthesis of 2-(4-bromophenyl)-1-(4-ethylphenyl) ethanone (Vc)</u>

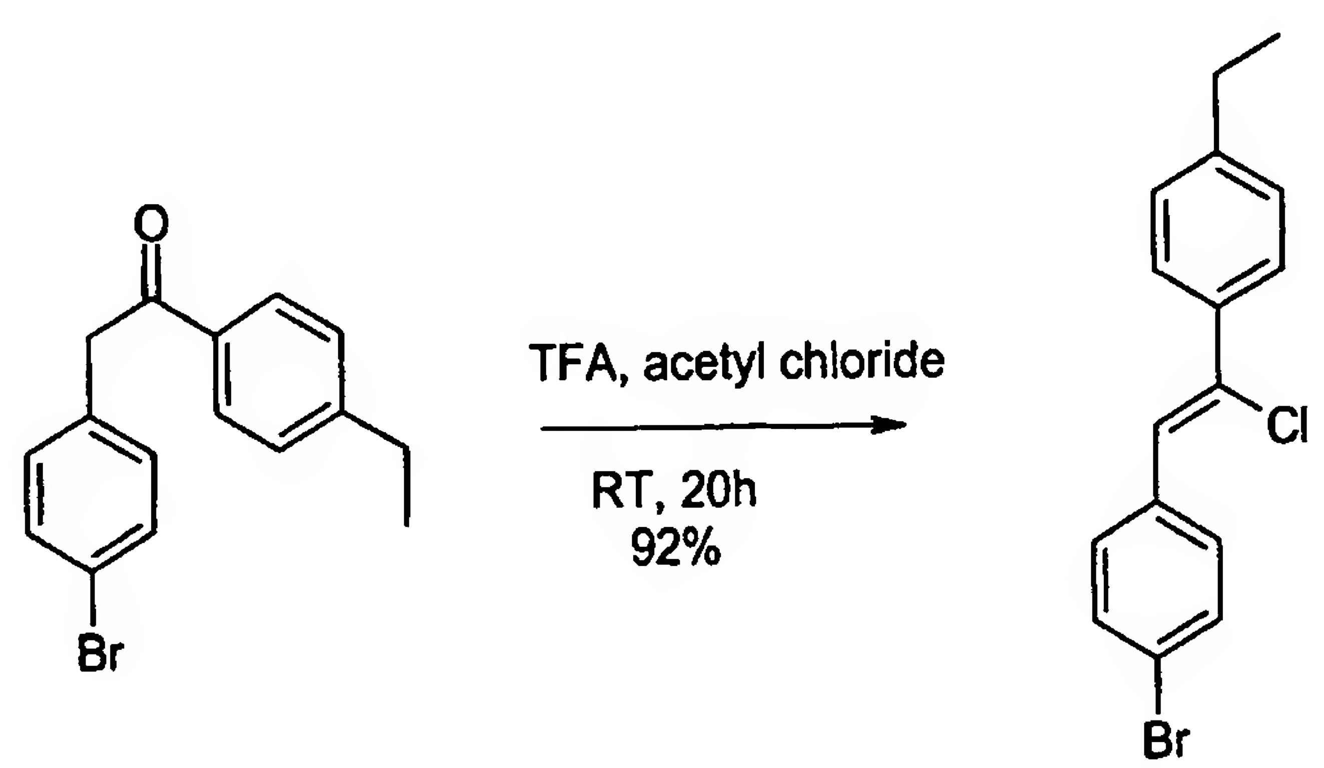


(IIIa) (Vc)

To a 50mL three-necked flask containing AlCl3 (7.305g; 54.79mmol) under N_2, ethyl benzene (IVc) (8.40mL; 68.48mmol) was added in one portion at RT. To this suspension (4-bromo-phenyl)-acetyl chloride (IIIa) (10.66g; 45.65mmol) was added drop wise keeping temperature below 40°C. Protocol and work-up was then similar with those described above. Title compound was obtained as a white powder (m=9.923g) in a 68% yield. Melting point: 146°C

1H-NMR (CDCl3=7.26ppm) : 7.92 (d, J=7.91 Hz, 2H), 7.44 (d, J=8.47 Hz, 2H), 7.28 (d, J=8.10 Hz, 2H), 7.13 (d, J=8.28 Hz, 2H), 4.21 (s, 2H), 2.70 (q, J=7.59 Hz, 2H), 1.25 (t, J=7.62 Hz, 3H)

b) <u>Step 2: Synthesis of 1-bromo-4- [(Z)-2-chloro-2- (4-ethylphenyl) vinyl] benzene (VIc)</u>

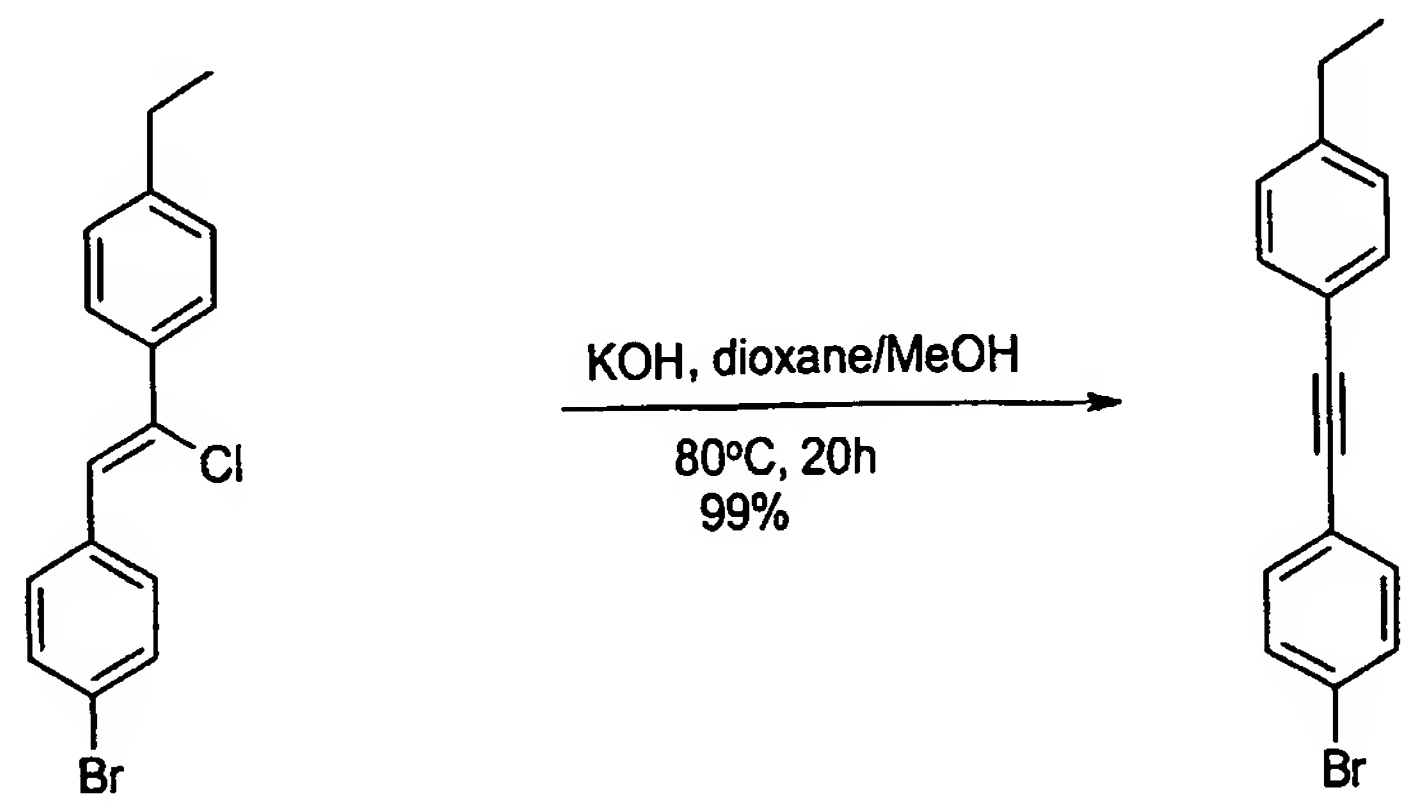


(Vc) (VIc)

In a 100mL flask, TFA (24.7mL; 322.8mmol) and acetyl chloride (18.34mL; 258.23mmol) were added in one portion into 2-(4-bromophenyl)-1-(4-ethylphenyl) ethanone (Vc) (9.787g; 32.28mmol) at RT. Protocol and work-up was then similar with those described above. The title compound (m= 9.60g) was obtained in a 92% yield. Melting point: 75°C

1H-NMR (CDCl3=7.26ppm) : 7.60 (d, J=7.53 Hz, 4H), 7.51 (d, J=8.66 Hz, 2H), 7.23 (d, J=8.28 Hz, 2H), 6.95 (s, 1H), 2.68 (q, J=7.59 Hz, 2H), 1.26 (t, J=7.53 Hz, 3H)

c) Step 4: Synthesis of 1-bromo-4-[(4-ethylphenyl) ethynyl] benzene(VIIc)

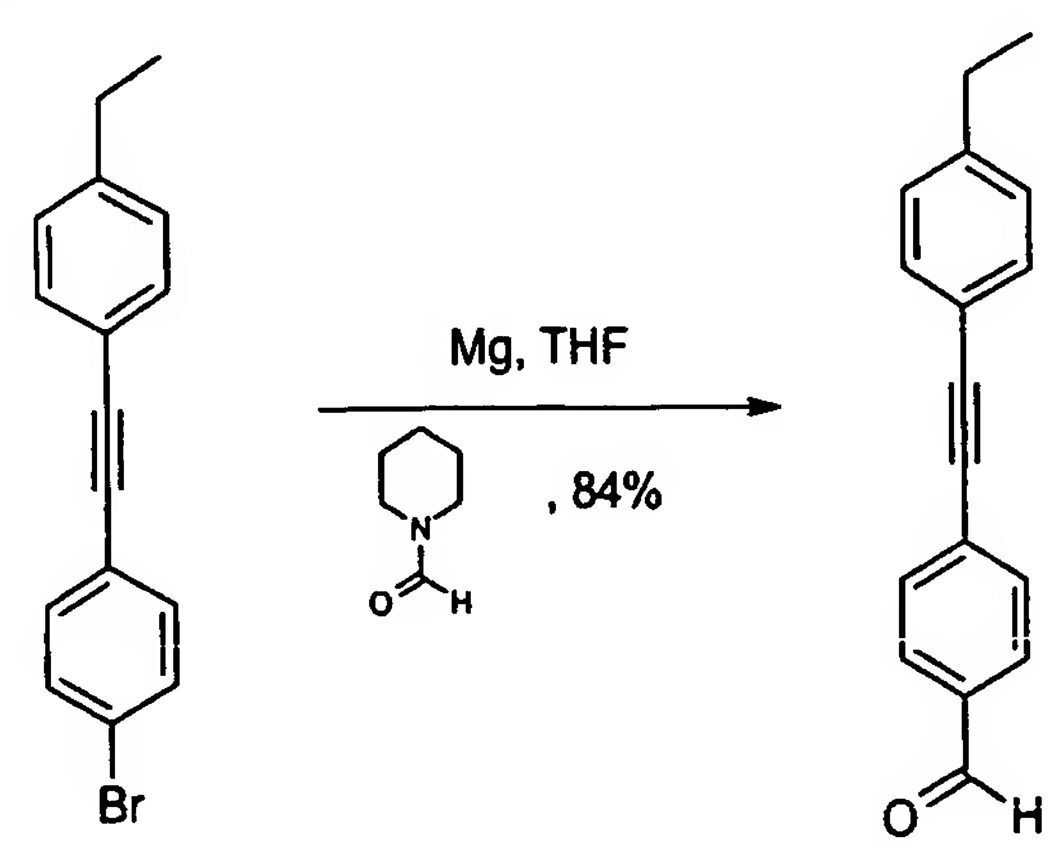


(VIc) (VIIc)

To a 100mL flask containing a solution of 1-bromo-4- [(Z)-2-chloro-2- (4-ethylphenyl) vinyl] benzene (VIc) (9.540g; 29.66mmol) in 1,4-dioxane (48mL; 5vols) and MeOH (14mL; 1.5vols), KOH (3.328g; 59.32mmol) was added in one portion. Protocol and work-up was then similar with those described above. Title compound (m=8.39g) was obtained in a 99% yield. Melting point: 117 °C

1H-NMR (CDCl3=7.26ppm) : 7.47 (d, J=8.66 Hz, 2H), 7.44 (d, J=8.28 Hz, 2H), 7.37 (d, J=8.47 Hz, 2H), 7.18 (d, J=8.10 Hz, 2H), 2.66 (q, J=7.59 Hz, 2H), 1.24 (t, J=7.62 Hz, 3H)

d) Step 4: Synthesis of 4-[(4-ethylphenyl) ethynyl] benzaldehyde (Ic)



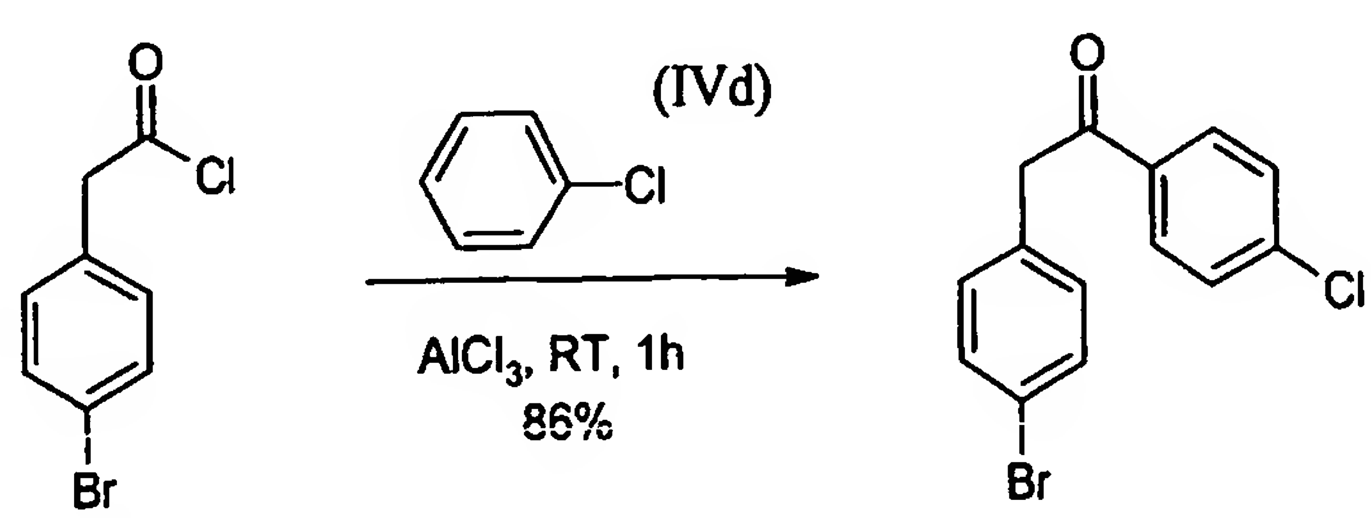
(VIIc) (Ic)

To a dry 100mL three-necked flask under a flow of N_2 containing magnesium turnings (0.782g; 32.17mmol) in dry THF (10mL) at reflux, an activating, small amount of 1-bromo-4- [(4-ethylphenyl) ethynyl] benzene (VIIc) (0.500g; 1.75mmol) was added in one portion. N_2 flow and stirring were stopped. Reaction mixture was heated at reflux for 5 minutes then iodine crystal was added keeping vigorous reflux to start the reaction. The reaction mixture went colourless after 5minutes and reaction mixture turned black-green after an additional minute. A solution of the remaining amount of 1-bromo-4- [(4-ethylphenyl) ethynyl] benzene (VIIc) (7.84g; 27.49mmol) in dry THF (30mL) was added drop wise into the reaction mixture while keeping gentle reflux. Reflux was maintained for 15minutes then temperature was allowed to cool to RT under stirring for 1h. The reaction mixture was cooled to 3°C and a solution of dry 1-formyl-piperidine (4.12mL; 43.87mmol) in dry THF (25mL) was added drop wise maintaining temperature at 5°C. The reaction mixture was then allowed to warm to room temperature (RT) and it was stirred overnight. Protocol and work-up was then similar with those described above. The title compound (m = 5.77g) was obtained as a cream solid in a 84% yield. Melting point: 89°C

1H-NMR (CDCl3=7.26ppm) : 10.0 (s, 1H), 7.86 (d, J=8.28 Hz, 2H), 7.66 (d, J=8.28 Hz, 2H), 7.47 (d, J=8.28 Hz, 2H), 7.21 (d, J=7.91 Hz, 2H), 2.68 (q, J=7.59 Hz, 2H), 1.25 (t, J=7.62 Hz, 3H)

Example 4: Preparation of 4-(4-chloro-phenylethynyl)-benzaldehyde

a) Step 1: Synthesis of 2-(4-bromophenyl)-1-(4-chlorophenyl) ethanone (Vd)



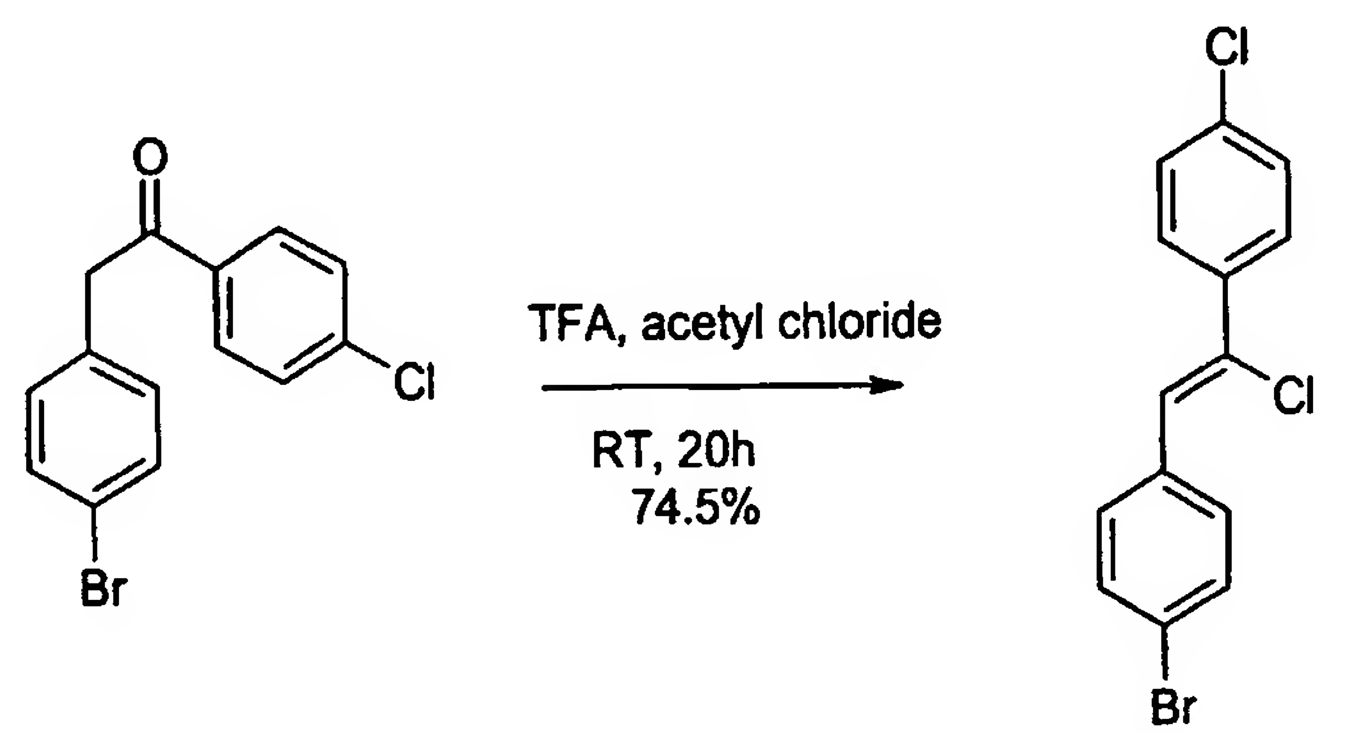
(IIIa) (Vd)

To a 100mL three-necked flask containing $AlCl_3$ (4.797g; 35.98mmol) under N_2, chlorobenzene (IVd) (36.6mL; 359.76mmol) was added in one portion at RT. To this suspension (4-bromo-phenyl)-acetyl chloride (IIIa) (7.0g; 29.98mmol) was added in one portion without cooling. Protocol and work-up was then similar with those described above. Title compound was obtained as a white powder (m=7.99g) in a 86% yield.

Melting point: 123°C

1H-NMR (CDCl3=7.26ppm) : 7.92 (d, J=8.66 Hz, 2H), 7.46 (d, J=4.89 Hz, 2H), 7.43 (d, J=5.27 Hz, 2H), 7.12 (d, J=8.47 Hz, 2H), 4.21 (s, 2H)

b) Step 2: Synthesis of 1-bromo-4-[(Z)-2-chloro-2-(4-chlorophenyl) vinyl] benzene (VId)



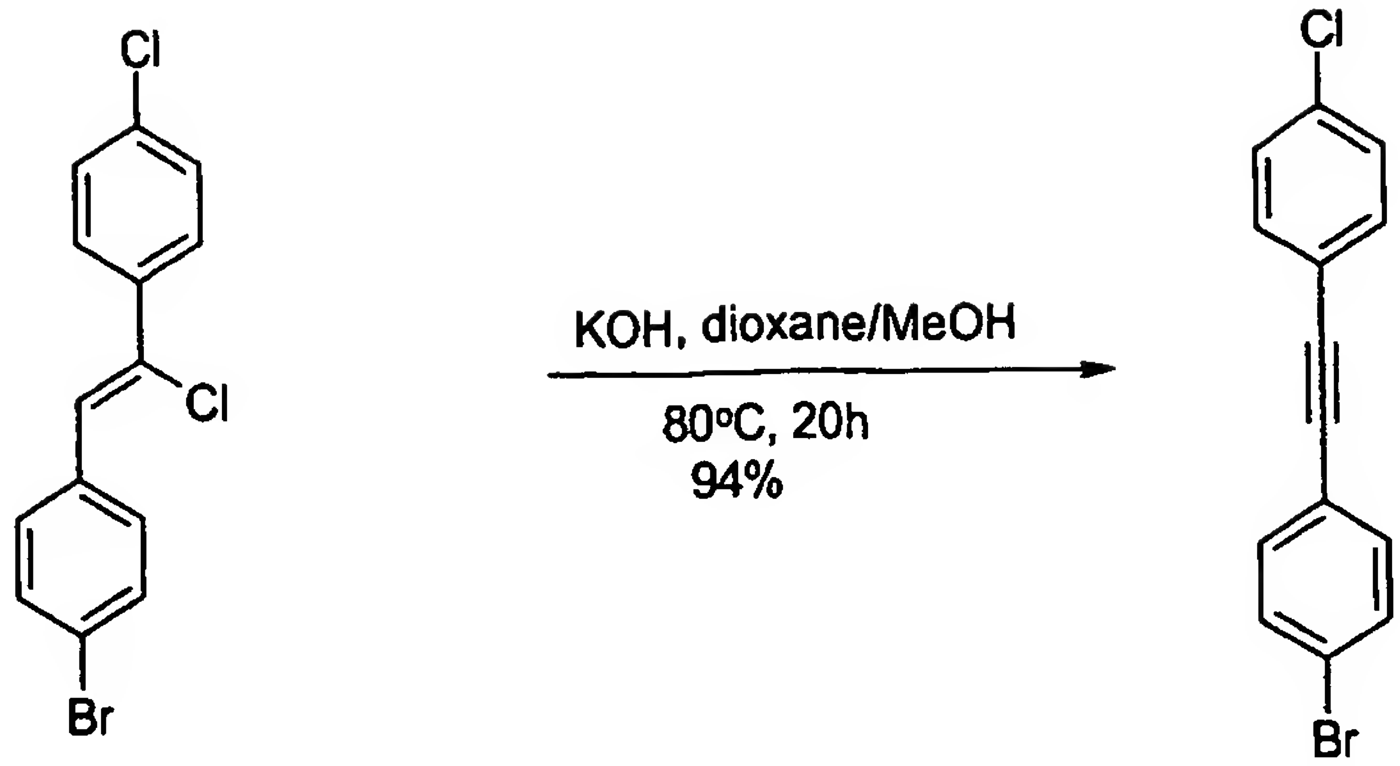
(Vd) (VId)

In a 250mL flask, TFA (24.7mL; 322.8mmol) and acetyl chloride (18.34mL; 258.23mmol) were added in one portion into 2-(4-bromophenyl)-1-(4-chlorophenyl) ethanone (Vd) (10.0g; 32.30mmol) at RT. Protocol and work-up was then similar with those described above. The title compound (m= 7.89g) was obtained in a 74.5% yield.

Melting point: 108 °C

1H-NMR (CDCl3=7.26ppm) : 7.62 (d, J=4.70 Hz, 2H), 7.59 (d, J=4.52 Hz, 2H), 7.52 (d, J=8.66 Hz, 2H), 7.37 (d, J=8.85 Hz, 2H), 6.96 (s, 1H)

c) Step 3: Synthesis of 1-bromo-4- [(4-chlorophenyl) ethynyl] benzene (VIId)

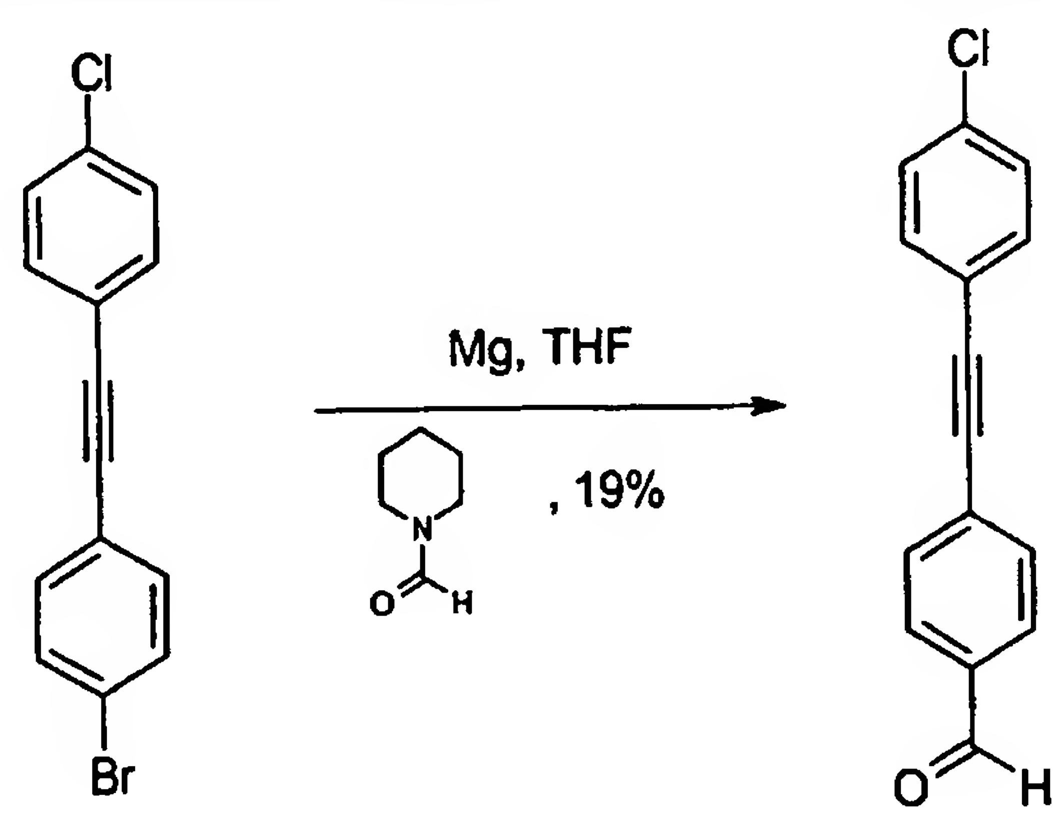


(VId) (VIId)

To a 100mL flask containing a solution of 1-bromo-4- [(Z) -2-chloro-2-(4-chlorophenyl) vinyl] benzene (VId) (7.89g; 24.05mmol) in 1,4-dioxane (40mL; 5vols) and MeOH (12mL; 1.5vols), KOH (2.699g; 48.10mmol) was added in one portion. Protocol and work-up was then similar with those described above. Title compound (m=6.598g) was obtained in a 94% yield. Melting point: 179 °C

1H-NMR (CDC13=7.26ppm) : 7.48 (d, J=8.47 Hz, 2H), 7.44 (d, J=8.66 Hz, 2H), 7.37 (d, J=8.47 Hz, 2H), 7.32 (d, J=8.66 Hz, 2H)

d) Step 4: Synthesis of 4-[(4-chlorophenyl) ethynyl] benzaldehyde (Id)



(VIId) (Id)

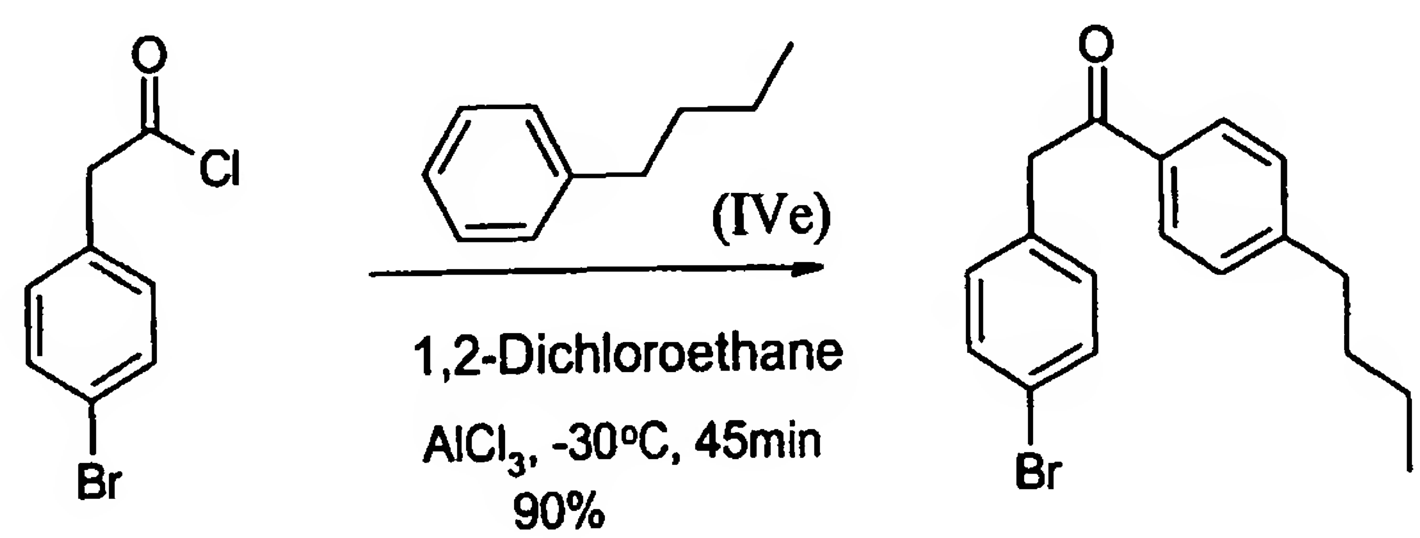
To a dry 100mL three-necked flask under a flow of N_2 containing magnesium turnings (0.595g; 24.50mmol) in dry THF (10mL) at reflux, an activating, small amount of 1-bromo-4- [(4-chlorophenyl) ethynyl] benzene (VIId) (0.39g; 1.33mmol) was added in one portion. N_2 flow and stirring were stopped. Reaction mixture was heated at reflux

for 5 minutes then iodine crystal was added keeping vigorous reflux to start the reaction. The reaction mixture went colourless after 5minutes and reaction mixture turned black-blue after an additional minute. A solution of the remaining amount of 1-bromo-4- [(4-chlorophenyl) ethynyl] benzene (VIId) (6.104g; 20.93mmol) in dry THF (35mL) at 55°C was added drop wise into the reaction mixture while keeping gentle reflux. Reflux was maintained for 15minutes then temperature was allowed to cool to RT under stirring for 1h. The reaction mixture was cooled to 3°C and a solution of dry 1-formyl-piperidine (3.71mL; 33.40mmol) in dry THF (10mL) was added drop wise maintaining temperature at 5°C. The reaction mixture was then allowed to warm to RT and it was stirred overnight. Protocol and work-up was then similar with those described above. Purification was performed by flash chromatography (SiO_2) using (cyclohexane 9-ethyl acetate 1). The title compound (m = 1.02g) was obtained as a white solid in a 19% yield. Melting point: 164°C

1H-NMR (CDCl3=7.26ppm) : 10.0 (s, J=- Hz, 1H), 7.87 (d, J=8.28 Hz, 2H), 7.66 (d, J=8.10 Hz, 2H), 7.48 (d, J=8.47 Hz, 2H), 7.35 (d, J=8.47 Hz, 2H)

Example 5: Preparation of 4-(4-butyl-phenylethynyl)-benzaldehyde

a) Step 1: Synthesis of 2-(4-bromophenyl)-1-(4-butylphenyl) ethanone (Ve)



(IIIa) (Ve)

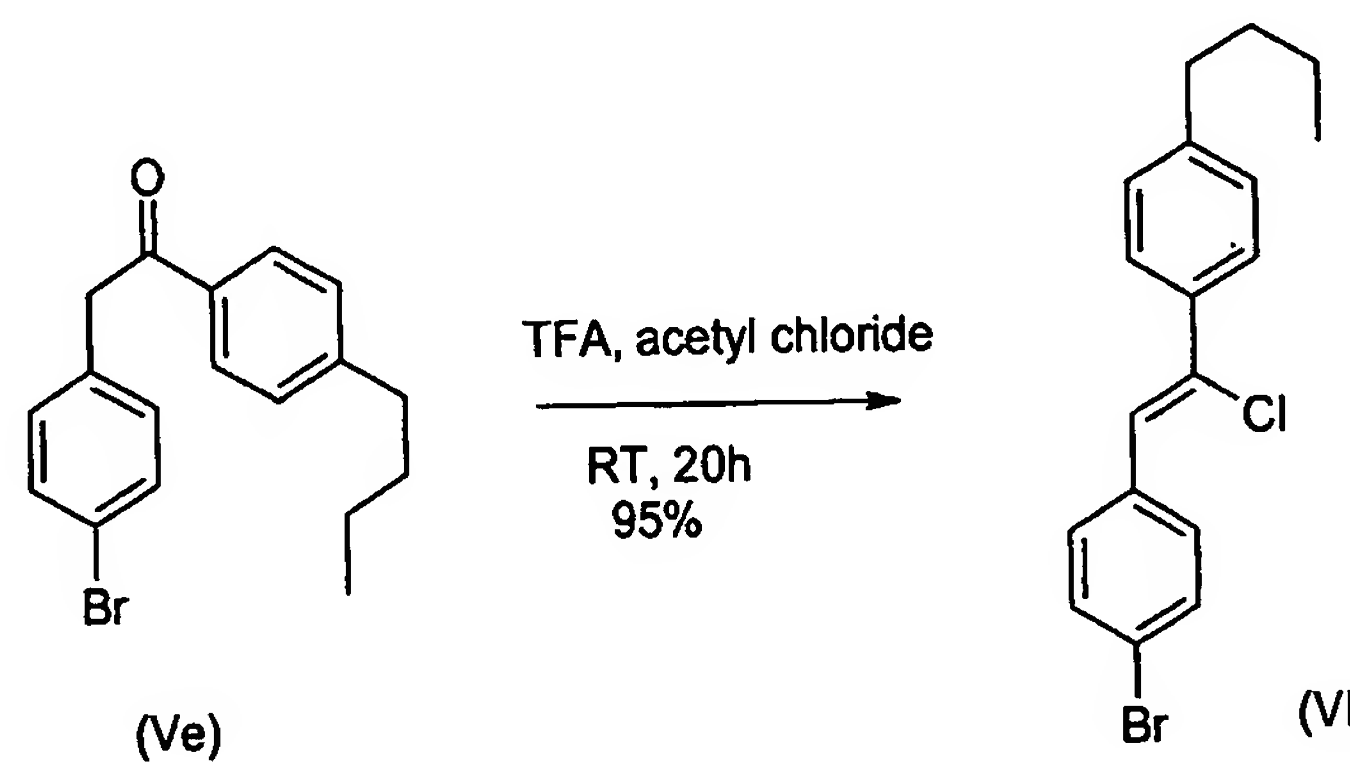
To a 1L three-necked flask containing $AlCl_3$ (40g, 0.299mol) in 1,2-dichloroethane (600mL) under N_2, butylbenzene (IVe) (49.7mL, 0.299mol) was added in one portion at -30°C. To this suspension (4-bromo-phenyl)-acetyl chloride (IIIa) (70g, 0.299mol) was added slowly over a period of 30min at such a rate that the internal temperature did not rise above -30°C. The reaction mixture was stirred at this temperature for 45min and poured into an ice-cold solution of 1.5M HCl (1000ml). The product was extracted into dichloromethane (2x500ml), washed with 10% sodium bicarbonate solution (500ml),

water, brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to obtain the titled compound as a white powder (m=90g) in a 90.9 % yield.

Melting point: 129.4°C-131.1°C

1H-NMR (CDCl3=7.26ppm): 1H-NMR 7.92 (d, J=8.16Hz, 2H), 7.45 (d, J=8.28Hz, 2H), 7.27 (d, J=8.22Hz, 2H), 7.14 (d, J=8.19Hz, 2H), 4.22 (s, 2H), 2.67 (t, J=7.47Hz, 2H), 1.62 (m, J= 7.38Hz, 2H), 1.37 (m, 2H), 0.93 (t, J= 7.29Hz, 3H)

b) Step 2: Synthesis of 1-bromo-4-[(Z)-2-chloro-2-(4-butylphenyl) vinyl] benzene (VIe)

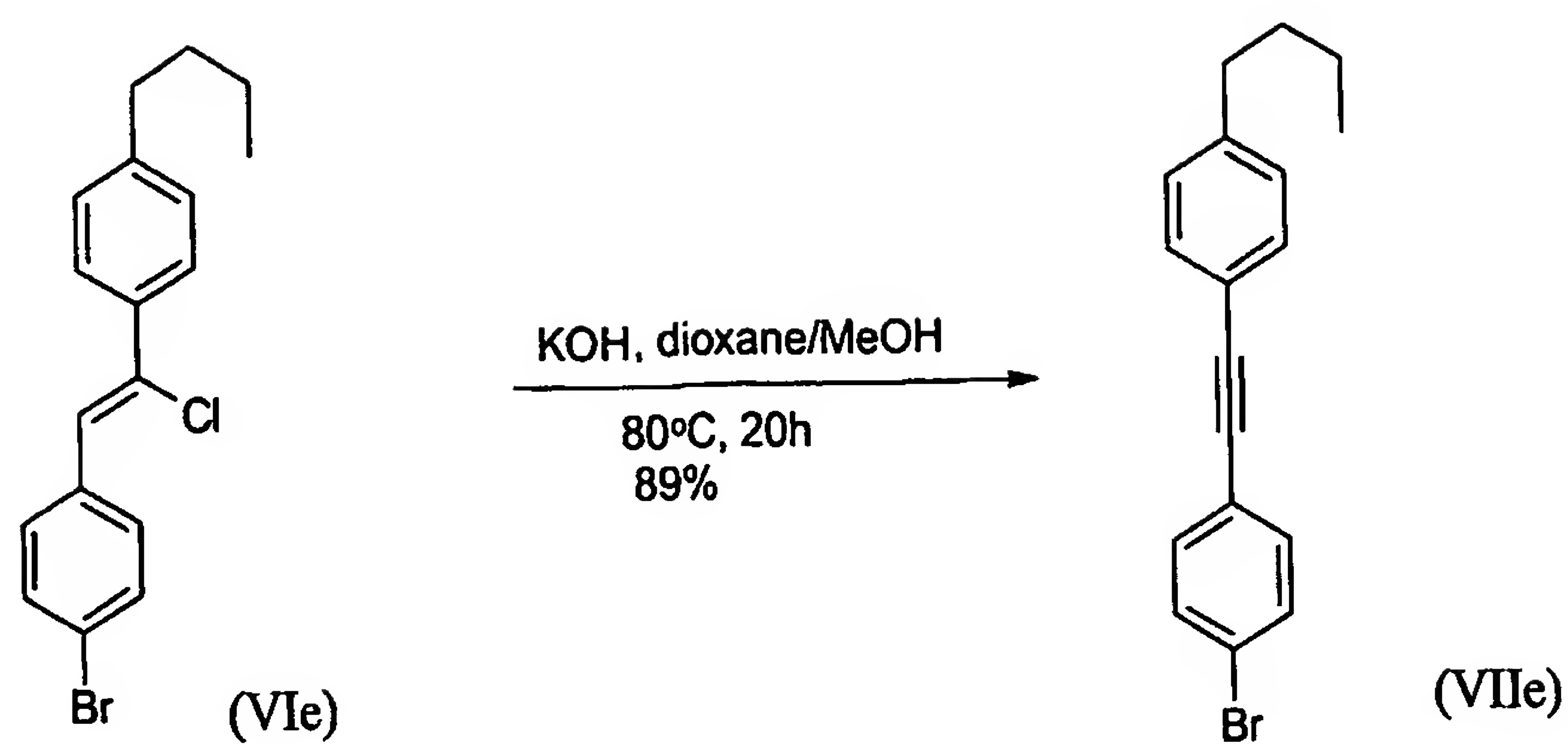


(Ve) (VIe)

To a 2L three-necked flask containing TFA (231mL, 3.01mol) and acetyl chloride (171.4mL, 2.41mol) was added in one portion 2-(4-bromophenyl)-1-(4-butylphenyl) ethanone (Ve) (100g; 0.301mol) at RT. The reaction mixture was stirred at room temperature overnight and work-up was then similar with those described above. The title compound (m= 100g) was obtained in a 95 % yield. Melting point:59-61°C

1H-NMR (CDCl3=7.26ppm) : 7.6 (m, , 4H), 7.52 (d, J=8.4Hz, 2H), 7.22 (d, J=8.01Hz, 2H), 6.97 (s, 1H), 2.65 (t, J=7.59Hz, 2H), 1.63 (m, J= 7.41Hz, 2H), 1.37 (m, 2H), 0.95 (t, J= 7.35Hz, 3H)

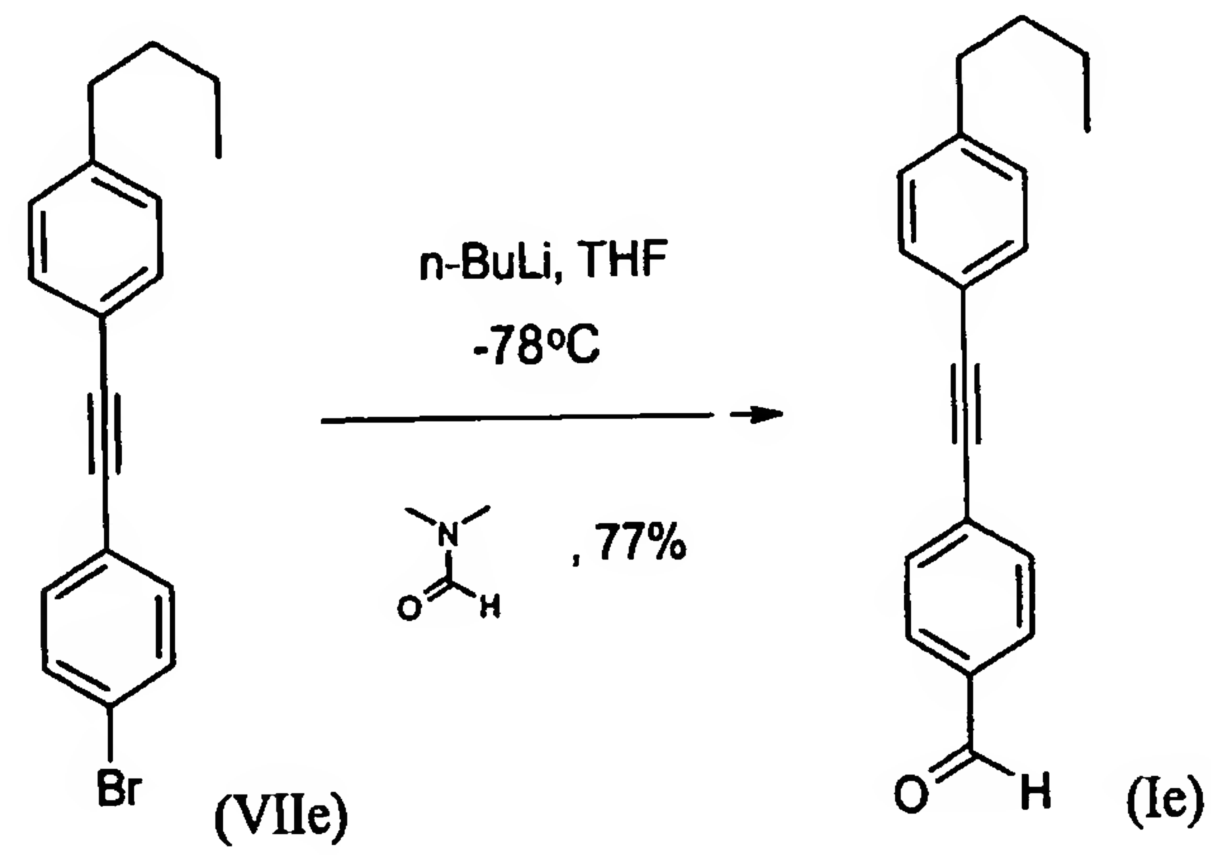
c) Step 3: Synthesis of 1-bromo-4- [(4-butylphenyl) ethynyl] benzene (VIIe)



To a 1L flask containing a solution of 1-bromo-4- [(Z) -2-chloro-2-(4-butyl-phenyl) vinyl] benzene (VIe) (100g; 0.285mol) in 1,4-dioxane (500mL; 5vols) and MeOH (200mL; 2vols), KOH (32g; 0.571mol) was added in one portion. Protocol and work-up was then similar with those described above. Title compound (m=80g) was obtained in a 89% yield. Melting point: 75.6-76.1 °C

1H-NMR (CDCl3=7.26ppm) : 7.4 (m, , 6H), 7.17(d, J=7.8Hz, 2H), 2.63 (t, J=7.56Hz, 2H), 1.63 (m, J= 7.38Hz, 2H), 1.38 (m, 2H), 0.95 (t, J= 7.2Hz, 3H)

d) Step 4: Synthesis of 4-[(4-butylphenyl) ethynyl] benzaldehyde (Ie)



To a dry 2L three-necked flask under a flow of N_2 containing 1-bromo-4- [(4-butylphenyl) ethynyl] benzene (VIIe) (100g; 0.319mol) in dry THF (1000mL) at -78°C was added n-BuLi (2.5M in hexane, 153.25mL, 0.383mol) and the reaction mixture was stirred at this temperature for 2h. The reaction mixture went dark-green after 5 minutes of the addition of butyl lithium. To this reaction mixture was added DMF (29.56mL,

0.383mol) and the resulting mixture was stirred for an additional 1h at -78°C. The reaction mixture turned black-blue after the addition of DMF. The reaction mixture was then quenched with 1.5M HCl (750ml) at this temperature and the product was extracted with MTBE (3X500mL). The combined organic layer were washed with 10% sodium bicarbonate solution (500ml), water, brine and dried. The solvent was evaporated under reduced pressure to afford the title compound (m = 65g) as a white solid in a 77% yield. Melting point: 76-78°C

1H-NMR (CDCl3=7.26ppm) : 10.02 (s, 1H), 7.86 (d, J=7.47Hz, 2H), 7.66 (d, J=7.98Hz, 2H), 7.47 (d, J=7.2Hz, 2H), 7.19 (d, J=7.68Hz, 2H), 2.64 (t, J=7.5Hz, 2H), 1.63 (quint, J= 7.2Hz, 2H), 1.36 (m, 2H), 0.94 (t, J= 7.2Hz, 3H)

The following further compounds may be obtained using the above set out protocols

Example 6:	4-p-Tolylethynyl-benzaldehyde
Example 7:	4-(4-Propyl-phenylethynyl)-benzaldehyde
Example 8:	4-(4-Cyclohexyl-phenylethynyl)-benzaldehyde
Example 9:	4-(4-Propoxy-phenylethynyl)-benzaldehyde
Example 10:	4-(4-Phenoxy-phenylethynyl)-benzaldehyde
Example 11:	4-Biphenyl-4-ylethynyl-benzaldehyde